AD_____

Award Number: DAMD17-03-P-0044

TITLE: Second Annual Diabetes Technology Meeting

PRINCIPAL INVESTIGATOR: David C. Klonoff, M.D.

CONTRACTING ORGANIZATION: Diabetes Technology Society
Foster City, California 94404

REPORT DATE: December 2002

TYPE OF REPORT: Final Proceedings

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	December 2002	Final Proceedings (31 Oct 02 - 2 Nov 02)

4. TITLE AND SUBTITLE
Second Annual Diabetes Technology Meeting

5. FUNDING NUMBERS
DAMD17-03-P-0044

6. AUTHOR(S)
David C. Klonoff, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Diabetes Technology Society
Foster City, California 94404

E-Mail: klonoff@diabetestechnology.org

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
Report contains color.

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 Words)*

The Second Annual Diabetes Technology Meeting on October 31 – November 2, 2002 at the Atlanta Hyatt Regency Hotel was co-sponsored by the Technologies for Metabolic Monitoring Joint Program, Centers for Disease Control and Prevention, NASA, Juvenile Diabetes Research Foundation International, the UC Berkeley Department of Bioengineering, the Georgia Tech/Emory Center for the Engineering of Living Tissues (GTEC), and by "Diabetes Technology & Therapeutics".

The Meeting included sessions on: 1) new technology for measuring glucose and other markers of glycemic control; 2) the artificial pancreas; 3) new technology for delivering insulin (and other therapeutic peptides) for diabetes, such as inhaled, oral, or by other new formulations; 4) computers and diabetes; and 5) a live demonstration of continuous glucose monitoring technology. The Meeting included two poster session receptions, in which a total of 99 posters were presented.

The Meeting, which began on the evening of October 31, 2002, was preceded on the afternoon of October 31, 2002 by two simultaneous half-day workshops, which were optional supplements to the meeting. These workshops were entitled: "Calibration of Continuous Glucose Sensors" and "Advances in therapy for diabetes - 2002". The 2 1/2 days of the meeting and workshops featured presentations by 50 diabetes technology experts.

14. SUBJECT TERMS
Glucose / Monitoring / Noninvasive / Telemedicine / Sensor

15. NUMBER OF PAGES
187

16. PRICE CODE

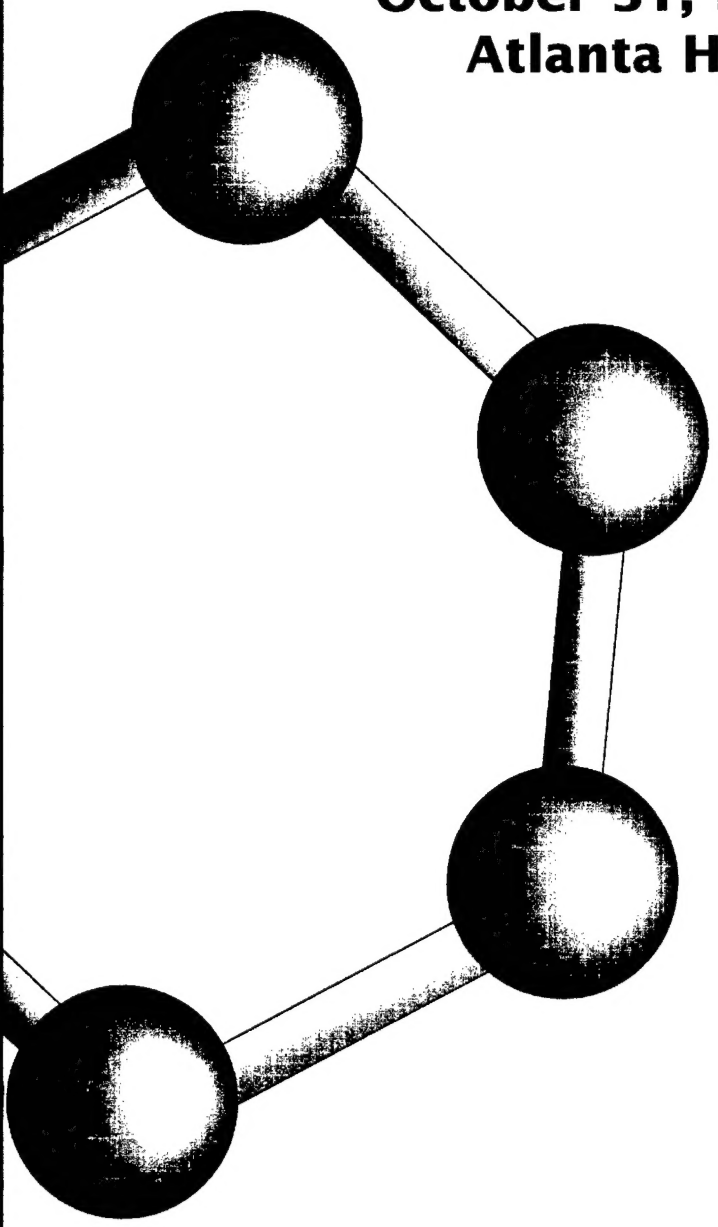
17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

DIABETES TECHNOLOGY SOCIETY

Applying science and engineering to fight diabetes

SECOND ANNUAL DIABETES TECHNOLOGY MEETING

October 31, November 1 & 2, 2002
Atlanta Hyatt Regency Hotel



Chair: David C. Klonoff, MD, FACP

In Collaboration with

- Centers for Disease Control and Prevention (CDC)
- National Aeronautics and Space Administration (NASA)
- Juvenile Diabetes Research Foundation International
- UC Berkeley Department of Bioengineering
- Georgia Tech / Emory Center for the Engineering of Living Tissues
- Technologies for Metabolic Monitoring Joint Program
- Diabetes Technology And Therapeutics
- Postgraduate Institute for Medicine
- The Center for Professional Distance Learning

Educational Grants Provided by

- Becton Dickinson and Company
- Bayer Diagnostics
- Lifescan, Inc.
- Eli Lilly and Company
- Medtronic MiniMed
- Metrika, Inc.
- Nobex Corporation
- Pfizer, Inc
- Roche Diagnostics
- TheraSense, Inc.

Drs. Jeffrey I. Joseph and Marc C. Torjman, Director and Associate Director, respectively, of the Artificial Pancreas Center at Thomas Jefferson University, have incorporated their annual Artificial Pancreas Meeting into this Diabetes Technology Meeting.

Second Annual Diabetes Technology Meeting

A showcase for the advanced development of technology for people with diabetes

October 31st, November 1 & 2, 2002
Atlanta Hyatt Regency Hotel

Presented by:

Diabetes Technology Society
1157 Chess Drive, Suite 100
Foster City, California 94404
Telephone 800.397.7755
Fax 650.349.6497
www.diabetestechnology.org

Welcome Letter

We are pleased to invite you to join us this Fall in Atlanta for the Second Annual Diabetes Technology Meeting on October 31 - November 2, 2002. This will be an excellent opportunity to meet leading scientists and learn about the latest technological advances for people with diabetes. Last year's sellout meeting in San Francisco brought together over 400 clinicians and scientists from 16 countries to focus on applying science and technology to fight diabetes.

The meeting's goal is to assemble technology developers and users to facilitate development of new and cost-effective tools to help people with diabetes - including an artificial pancreas. This year we will be adding a session on applications of computers in diabetes therapy, including case management, telemedicine, metabolic modeling, educational tools, software, and hardware. Scientists and clinicians will have plenty of opportunities to share ideas in both formal and informal settings and gain insight into how to help decrease the physical and psychological burden of diabetes.

The format will include: state-of-the-art lectures, oral presentations of Abstracts, panel discussions with Q&A sessions, a live demonstration of continuous glucose monitoring, and two poster sessions. A syllabus of the submitted Abstracts will be distributed to all attendees. We have received 130 Abstracts. In addition to breakfast, lunch, and two snack breaks each day, there will be two evening receptions/poster sessions for informal discussions. These include a reception on October 31 (which will mark the meeting's commencement) and a second reception on the evening of November 1.

On the afternoon of October 31, 2002, prior to the meeting, we will present two concurrent optional workshops (with separate registration) entitled, "New Therapy for Diabetes – 2002" and "Calibration of Continuous Glucose Sensors". Guided tours of the Georgia Tech Department of Bioengineering will also be conducted for attendees of the meeting on that day.

We look forward to seeing you in Atlanta and sharing information about projects of mutual interest.

With best wishes,
David C. Klonoff, M.D.
Chair, Diabetes Technology Meeting Planning Committee
Clinical Professor of Medicine, UCSF

Acknowledgements

The Diabetes Technology Meeting is presented by the Diabetes Technology Society.

In Collaboration with

- Centers for Disease Control and Prevention (CDC)
- National Aeronautics and Space Administration (NASA)
- Juvenile Diabetes Research Foundation International
- UC Berkeley Department of Bioengineering
- Georgia Tech / Emory Center for the Engineering of Living Tissues
- Technologies for Metabolic Monitoring Joint Program
- Diabetes Technology And Therapeutics
- Postgraduate Institute for Medicine
- The Center for Professional Distance Learning

Educational Grants Provided by

- Becton Dickinson and Company
- Bayer Diagnostics
- Lifescan, Inc.
- Eli Lilly and Company
- Medtronic MiniMed
- Metrika, Inc.
- Nobex Corporation
- Pfizer, Inc.
- Roche Diagnostics
- TheraSense, Inc.

The Workshop "Calibration of Continuous Glucose Sensors" is supported by educational grants from Disetronic Medical Systems, Inc. and Roche Diagnostics and also by educational grants from Lifescan, Inc., Medtronic MiniMed, Pendragon Medical Ltd., Sensors for Medicine and Science, Inc., SpectRx, Inc., and TheraSense, Inc.

Table of Contents

Course Faculty

Planning Committee

Chair

- David C. Klonoff, MD, FACP - *UC San Francisco, CA*

Faculty

- Riccardo Bellazzi, PhD - *University of Pavia, Italy*
- Gerold Grodsky, PhD - *UC San Francisco, CA*
- Richard Guy, PhD - *University of Geneva, Switzerland*
- Michael Hopmeier, MSME - *Unconventional Concepts, Inc., Washington, D.C.*
- Jeffrey Joseph, DO - *Thomas Jefferson University, Philadephia, PA*
- Dorian Liepmann, PhD - *UC Berkeley, CA*
- Neal Pellis, PhD - *NASA Johnson Space Center, Houston, TX*
- Athanassios Sambanis, PhD - *Georgia Institute of Technology, Atlanta, GA*
- Celine Tamir, RN - *Diabetes Technology Society, Foster City, CA*
- Marc Torjman, PhD - *Thomas Jefferson University, Philadephia, PA*

Moderators

- V. Michelle Chenault, PhD, MT(ASCP) - *U.S. Food and Drug Administration, Rockville, MD*
- Judith Fradkin, MD, - *National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD*
- Karl Friedl, PhD, - *U.S. Army, Fort Detrick, MD*
- Richard Furlanetto, MD, PhD, - *Juvenille Diabetes Research Foundation International, New York, NY*
- Robert Gabbay, MD, PhD, - *Pennsylvania State University, Hershey, PA*
- Gerold Grodsky, PhD, - *UC San Francisco, CA*
- Richard Guy, PhD, - *University of Geneva, Switzerland*
- Jeffrey I. Joseph, DO, - *Thomas Jefferson University, Philadelphia, PA*
- David C. Klonoff, MD, FACP - *UC San Francisco, CA*
- Dorian Liepmann, PhD, - *UC Berkeley, CA*
- Neal R. Pellis, PhD, - *NASA Johnson Space Center, Houston, TX*
- Kimberly Porter, PhD, RD, L.D, - *Centers for Disease Control and Prevention, Atlanta, GA*
- Marc J. Torjman, PhD, - *Thomas Jefferson University, Philadelphia, PA*

Faculty

- Garth E. Austin, MD, PhD - Emory University, Atlanta, GA
- Riccardo Bellazi, PhD - University of Pavia, Pavia, Italy
- B. Wayne Bequette, PhD - Rensselaer Polytechnic Institute, Troy, NY
- Kathy J. Berkowitz, CDE, FNP, RN - Grady Health System, Atlanta, GA
- Lawrence Blonde, MD - Ochsner Clinic Foundation, New Orleans, LA
- Bruce W. Bode, MD - Atlanta Diabetes Associates, Atlanta, GA
- Patrick H. Bowen, MD - Emory University, Atlanta, GA
- Bruce Buckingham, MD - Lucile Packard Children's Health Services, Stanford, CA
- Andreas Caduff, MSc - Pendragon Medical, Zurich, Switzerland
- Anthony Czarnik, PhD - Sensors for Medicine and Science, Inc., Germantown, MD
- Mark Faupel, PhD - SpectRx, Inc., Norcross, GA
- Benjamin Feldman, PhD - TheraSense, Inc., Alameda, CA
- Suzanne S.P. Gebhart, MD - Emory University, Atlanta, GA
- Barjor Gimi, MSc - University of Illinois at Chicago, Chicago IL
- David A. Gough, PhD - University of California San Diego, La Jolla, CA
- Steven Gutman, MD, MBA - U.S. Food and Drug Administration, Rockville, MD
- Richard Guy, PhD - University of Geneva, Geneva Switzerland
- Lutz Heinemann, PhD - Profil Institute for Metabolic Research, Neuss, Germany
- Michael Hopmeier, MSc - Unconventional Concepts, Inc., Washington, D.C.
- David L. Horwitz, MD, PhD - LifeScan, Inc., Milpitas, CA
- Benjamin R. Irvin, PhD - Metrika, Inc., Sunnyvale, CA
- Karsten Jungheim, MD - German Diabetes Research Institute, Duesseldorf, Germany
- Frederick L. Kiechle, MD, PhD - William Beaumont Hospital, Royal Oak, MI
- William Landschulz, MD, PhD - Pfizer Global Research & Development, New London, CT
- Beth L. Laube, PhD - John Hopkins University, Baltimore, MD
- Volker Lodwig, PhD - Roche Diagnostics GmbH, Mannheim, Germany
- Alfred E. Mann - MannKind Corporation, Sylmar, CA
- Ronald C. Merrell, MD -Virginia Commonwealth University, Richmond, VA
- Stephen L. Monfre, PhD - Sensys, Inc., Chandler, AZ
- Jerry Palmer, MD - University of Washington, Seattle, WA
- John C. Pickup, MD, PhD - Guy's Hospital, London, England
- Gerard Reach, MD - INSERM U341, Hospital Avicenne, Paris
- Kerstin Rebrin, MD, PhD - Medtronic MiniMed, Northridge, CA
- Bruno Reihl, PhD - Diesetronic Medical Systems, Inc., Burgdorf, Switzerland
- Athanassios Sambanis, PhD - Georgia Institute of Technology, Atlanta, GA
- Eric J. Sampson, PhD - Centers for Disease Control and Prevention, Atlanta, GA
- Viren Sarin, PhD - Eli Lilly and Company, Indianapolis, IN
- Peter Scanlon, MD - Cheltenham General Hospital, Cheltenham, England
- Marina Scavini, MD - University of New Mexico, Albuquerque, NM
- Meinhard Schmidt, MSEE - Roche Diagnostics GmbH, Mannheim, Germany
- Matthias Steine, PhD - Inverness Medical Ltd., Inverness, Scotland
- J. Gordon Still, MD, PhD - Nobex Corporation, Research Triangle Park, NC
- William V. Tamborlane, MD - Yale University, New Haven, CT
- William Van Antwerp, MSME - Medtronic MiniMed, Northridge, CA
- Collin Weber, MD, DMSci - Emory University, Atlanta, GA
- Howard A. Wolpert, MD - Joslin Diabetes Center, Boston, MA

Faculty Disclosure

The Postgraduate Institute for Medicine has a conflict of interest policy that requires course faculty to disclose any real or apparent commercial financial affiliations related to the content of their presentations/materials. It is not assumed that these financial interests or affiliations will have an adverse impact on faculty presentations; they are simply noted here to fully inform participants.

Disclosed Relationship(s) with Industry

- Ricardo Bellazzi, PhD - Partners in EU grant with Roche Diagnostics
- Bruce Bode, MD - Grants/Research Support: Medtronic MiniMed, TheraSense, Inc., Consultant: Medtronic MiniMed, TheraSense, Inc., Speakers' Bureau: Eli Lilly & Co., Medtronic MiniMed, Pfizer Inc
- Bruce Buckingham, MD - Grants/Research Support: Medtronic MiniMed, Cygnus
- Andreas Caduff - Stockholder: Pendragon Medical AG
- Anthony W. Czarnik, PhD - Stockholder: Sensors for Medicine & Science, Inc.
- Mark Faupel, PhD - Executive Vice President and Chief Technical Officer of SpectRx, Inc., Stockholder: Roche Diagnostics
- Benjamin Feldman, PhD - Employee of TheraSense, Inc.
- Suzanne Gebhart, SP, MD - Grants/Research Support: Eli Lilly & Co., Bayer, Pfizer Inc, Speakers' Bureau: Bayer, Pfizer Inc.
- David A. Gough, PhD - Patent Royalties
- Steven Gutman, MD, MBA - Employee, U.S. Food & Drug Administration
- Lutz Heinemann, PhD - Grants/Research Support and Consultant: Roche Diagnostics, Pendragon, NovoNordisk, Eli Lilly & Co., Medtronic MiniMed, Pfizer Inc.
- David L. Horwitz, MD, PhD - Employee of Johnson & Johnson - LifeScan, Inc
- Benjamin R. Irvin, PhD - Employee and Stockholder of Metrika, Inc.
- David C. Klonoff, MD - Grants/Research Support: Aerogen, Amylin Pharmaceuticals, Antares Pharma, Inc., Pfizer Inc, Restoragen Inc., Metrika, Inc. Consultant:, OptiScan Biomedical
- William Landschulz, MD - Employee of Pfizer Inc
- Beth L. Laube, PhD - Grants/Research Support: Inhale Therapeutic Systems, Consultant: Inhale Therapeutic Systems, Inc.
- Volker Lodwig, PhD - Employee of Roche Diagnostics
- Alfred E. Mann - Employee of MannKind Corporation
- Stephen L. Monfre, PhD - Employee of Instrumentation Metrics, Inc.
- Jerry Palmer, MD - Consultant: Pfizer Inc., Bayer, Eli Lilly & Co.
- Kerstin Rebrin, MD, PhD - Employee of Medtronic MiniMed
- Bruno Reihl, PhD - Employee of Disetronic Medical Systems
- Peter Scanlon, MD - Grants/Research Support; Consultant: Eli Lilly & Co.
- Meinhard Schmidt, MSEE - Employee of Roche Diagnostics
- Matthias Steine, PhD - Employee of LifeScan, Inc. - Inverness Medical Ltd
- James Gordon Still, MD, PhD - Stockholder, Employee: Nobex Corp.
- William V. Tamborlane, MD - Grants/Research Support; Consultant; Speakers' Bureau: Medtronic MiniMed
- William Van Antwerp, PhD - Employee of MedtronicMiniMed

Faculty Disclosure, Continued

No Actual or Potential Conflict

- Garth E. Austin, MD
- Wayne B. Bequette, PhD
- Kathy Berkowitz, CDE, FNP, RN
- V. Michelle Chenault, PhD
- Judith Fradkin, MD
- Richard Furlanetto, MD, PhD
- Robert Gabbay, MD, PhD
- Gerold Grodsky, PhD
- Richard Guy, PhD
- Michael Hopmeier, MSME
- Frederick L. Kiechle, MD, PhD
- Ronald C. Merrell, MD
- Neal R. Pellis, PhD
- John C. Pickup, MD, PhD
- Kimberly Porter, PhD, RD, LD
- Gerard Reach, MD
- Eric J. Sampson, PhD
- Marc C. Torjman, MD
- Collin Weber, MD

Will Disclose All Financial Relationships Prior to Presentation:

- Lawrence Blonde, MD
- Patrick H. Bowen, MD
- Jeffrey I. Joseph, DO
- Dorian Liepmann, PhD
- Athanassios Sambanis, PhD
- Marina A. Scavini, MD, PhD
- Howard Wolpert, MD

Educational Objectives

Diabetes Technology Meeting

By attending the Second Annual Diabetes Technology Meeting, participants will meet the top scientists and clinicians who are developing new technology for diabetes and should be able to:

- Understand the advantages and limitations of continuous glucose monitoring.
- Identify situations to perform or avoid alternate site glucose testing.
- Distinguish an artificial and a bioartificial pancreas.
- Recognize the challenges for delivering insulin without needles.
- Learn how to use the Internet for providing diabetes healthcare.

"New Therapy for Diabetes - 2002" Optional Workshop

By attending the "New Therapy for Diabetes - 2002" Workshop, participants will be able to explore the newest treatments available for people with diabetes, and they will be able to:

- Identify mechanisms of action of new oral agents for diabetes.
- Identify potential serious side effects of new oral agents for diabetes.
- Review currently available insulin preparations.
- Identify methods to decrease the risk of cardiovascular disease in diabetes.
- Discover new gut peptides for treating diabetes.
- Describe benefits and risks of islet cell transplantation and whole pancreas transplantation for type 1 diabetes.

"Calibration of Continuous Glucose Sensors" Optional Workshop

By attending the "Calibration of Continuous Glucose Sensors" Workshop participants will review the newest technologies for measuring glucose on a continuous basis as well as:

- Identify safe and effective technologies for continuous glucose measurement.
- Understand why continuous glucose sensors require regular recalibration.
- Recognize advantages and disadvantages of implanted vs. external continuous glucose sensors.
- Know optimal methods for calibration of glucose sensors.
- Understand the clinical settings where continuous glucose monitoring is desirable.

Accreditation Statement

Physicians:

This activity has been approved for AMA PRA credit for a total of 17.5 credit hours (15 credit hours for the Meeting and 2.5 credit hours for one workshop: "New Therapy in Diabetes - 2002").

Nurses:

This educational activity for a total of 21.3 contact hours (18.2 hours total meeting and 3.1 hours for one workshop: "New Therapy for Diabetes - 2002") is provided by Postgraduate Institute for Medicine. Postgraduate Institute for Medicine is approved as a provider of continuing education in nursing by the by the Colorado Nurses' Association, which is accredited as an approver of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation. The Postgraduate Institute for Medicine is approved by the California Board of Registered Nursing, Provider Number 13485 for 18.2 contact hours (18.2 hours total meeting and 3.1 hours for one workshop:"New Therapy for Diabetes 2002")

Agenda • Thursday, October 31, 2002

Two Optional Concurrent Pre-Meeting Workshops

Workshop I: Calibration of Continuous Glucose Sensors

Session A - Clinical Perspectives

International Ballroom North

12:30 PM Moderator
V. Michelle Chenault, Ph.D.
U.S. Food and Drug Administration, Rockville, Maryland

12:35 PM Lutz Heinemann, Ph.D., Profil Institut for Metabolic Research, Neuss, Germany
Calibration and Continuous Glucose Monitoring: An Elusive Goal?

12:55 PM Gerard Reach, M.D., Hospital Avicenne, Paris, France
Critical Issues in the Calibration of a System Sensing Glucose in Interstitial Fluid

1:15 PM David Gough, Ph.D., University of California, San Diego
The Implantable Glucose Sensor: What's "Easy" and What's Not

1:35 PM Frederick Kiechle, M.D., Ph. D., William Beaumont Hospital, Royal Oak, Michigan
Clinical Pathologist's View of Continuous Glucose Sensor Calibration

1:55 PM Bruce Buckingham, M.D., Lucile Packard Children's Hospital, Stanford, California
Clinical Issues in Calibrating Sensors

2:15 PM Panel Discussion and Question & Answer

2:40 PM Break

Session B - Industry Perspectives

International Ballroom North

3:05 PM Moderator
Gerold Grodsky, Ph.D., University of California, San Francisco

3:10 PM Bruno Reihl, Ph.D., Disetronic Medical Systems, Burgdorf, Switzerland
Calibration Procedures for Subcutaneous Glucose Monitors

3:20 PM Matthias Stiene, Ph.D., Inverness Medical Ltd., Inverness, Scotland
Factors Impacting the Calibration of Continuous Monitoring Systems

3:30 PM William Van Antwerp, M.S., Medtronic MiniMed, Northridge, California
Calibration of Subcutaneous Glucose Sensing

3:40 PM Andreas Caduff, M.Sc., Pendragon Medical, Zurich, Switzerland
A Novel Continuous Glucose Monitoring System Based on Impedance Spectroscopy: the Calibration Procedure

3:50 PM Volker Lodwig, Ph.D., Roche Diagnostics GmbH, Mannheim, Germany
New Assessment Criteria for Continuous Glucose Monitoring

4:00 PM Anthony Czarnik, Ph.D., Sensors for Medicine and Science, Inc., Germantown, Maryland
The SMSI Continuous Glucose Sensing System

4:10 PM Mark Faupel, Ph.D., SpectRx, Inc., Norcross, Georgia
Calibration of Glucose Measurements Made in Transdermal Body Fluid Accessed via Micropores in the Stratum Corneum of the Skin

4:20 PM Benjamin Feldman, Ph.D., TheraSense, Inc., Alameda, California
Calibration Considerations for a 3-day Implantable Sensor

4:30 PM Panel Discussion and Question and Answer

5:45 PM End of Workshop

Workshop II: New Therapy for Diabetes - 2002

International Ballroom South

2:00 PM Introduction
Robert Gabbay, M.D., Ph.D., Pennsylvania State University, Hershey, Pennsylvania

2:05 PM Suzanne Gebhart, M.D., Emory University, Atlanta, Georgia
New Insulin & Insulin Analogs & Other Peptide Treatments of Diabetes

2:35 PM Patrick Bowen, Emory University, Atlanta, Georgia
Current and Future Oral Agents for Type 2 Diabetes

3:05 PM Panel Discussion and Question & Answer

3:20 PM Break

3:45 PM Kathy Berkowitz, RN, CS, FNP, CDE, Grady Health System, Atlanta, Georgia
New Therapies & New Technology: Does It Replace Lifestyle Management? An Educator's Perspective

4:15 PM Collin Weber, M.D., D.M.Sci. Emory University, Atlanta, Georgia
Prospects for Large Scale Islet Transplantation

4:45 PM Panel Discussion and Question & Answer

5:00 PM End of Workshop

Second Annual Diabetes Technology Meeting Begins

12:00-8:00 PM Registration — Embassy Hall

6:00- 8:00 PM Welcome Reception — Embassy Hall
Poster Presentations

8:00-10:00 PM Posters Remain on Display for Viewing

Agenda • Friday, November 1, 2002

7:00 AM Registration — Embassy Hall

7:00 AM Continental Breakfast — Embassy Hall

Session I - New Methods for Measuring Glucose and Other Analytes for Diabetes

8:00 AM Welcome — International Ballroom
David C. Klonoff, M.D., University of California, San Francisco

8:05 AM Moderator
Kimberly Porter, Ph.D., Centers for Disease Control and Prevention, Atlanta, Georgia

8:10 AM Eric Sampson, Ph.D., Centers for Disease Control and Prevention, Atlanta, Georgia
Keynote Address: Current Activities at CDC National Diabetes Laboratory

8:30 AM Michael Hopmeier, M.S.M.E., Unconventional Concepts, Inc. Washington, D.C.
The Joint DOD / NASA / NIH / JDRF Technologies for Metabolic Monitoring (TMM) Program

8:50 AM Stephen Monfre, Ph.D., Sensys Medical, Inc., Chandler, Arizona
Update on the Clinical Progress of a Non- Invasive Blood Glucose Monitor

9:10 AM Barjor Gimi, Department of Bioengineering, University of Illinois at Chicago
Non-Invasive Monitoring of Encapsulated Beta Cell Function Using Mn2+-Enhanced Magnetic Resonance Imaging

9:30 AM Panel Discussion and Question & Answer

9:50 AM Break Embassy Hall

10:30 AM Moderator
Karl Friedl, Ph.D., US Army, Fort Detrick, Maryland

10:35 AM Benjamin Feldman, Ph.D., TheraSense, Inc., Alameda, California
A 3-day Subcutaneous Glucose Sensor Based on Wired EnzymeTM Technology: Evaluation in People with Diabetes

10:55 AM Meinhard Schmidt, M.S.E.E., Roche Diagnostics GmbH, Mannheim, Germany
From Spot Monitoring to the Automated Pancreas - Technology Roadmap to Advanced Diabetes Management

11:15 AM Garth Austin, M.D., Ph.D., Emory University, Atlanta, Georgia
Clinical Measurement of Long Term Glycemic Control in Diabetic Patients

11:35 AM Ben Irvin, Ph.D., Metrika, Inc., Sunnyvale, California
New Technology for Improving Access to Immediate A1C Results

11:55 AM Panel Discussion and Question & Answer

12:15 PM Lunch Regency VII

Session II - Artificial Pancreas Symposium: Glucose Monitoring, Insulin Delivery, and Feedback Control

1:25 PM Moderators and Co-Chairs International Ballroom
Jeffrey Joseph, D.O., Thomas Jefferson University, Philadelphia, Pennsylvania
Marc Torjman, Ph.D., Thomas Jefferson University, Philadelphia, Pennsylvania

1:30 PM John Pickup, M.D., Ph.D., Guy's Hospital, London, England
In-vivo Glucose Sensing: Clinical Practice and Research

1:50 PM Gerard Reach, M.D., Hospital Avicenne, France
Prevention of Hypoglycemia Using Risk Assessment with a Continuous Glucose Monitoring System

2:10 PM William Tamborlane, Ph.D., Yale University, New Haven, Connecticut
Diabetes Research in Children Network (DirecNet):
Testing Sensor Technology in Youth with Type 1 Diabetes

2:30 PM Marina Scavini, M.D., Ph.D., University of New Mexico, Albuquerque, New Mexico
Optimal Artificial Delivery for an Artificial Pancreas

2:50 PM Panel Discussion and Question & Answer

3:10 PM Break Embassy Hall

3:50 PM Moderators and Co-Chairs
Jeffrey Joseph, D.O., Thomas Jefferson University, Philadelphia, Pennsylvania
Marc Torjman, Ph.D., Thomas Jefferson University, Philadelphia, Pennsylvania

3:55 PM Kerstin Rebrin, M.D., Ph.D., Medtronic MiniMed, Northridge, California
Various Approaches for Closed-Loop Insulin Delivery

4:15 PM Bruno Reihl, Ph.D., Disetronic Medical Systems, Burgdorf, Switzerland
Concept and Realization of a Control-loop Application for the Automated Delivery of Insulin

4:35 PM B. Wayne Bequette, Ph.D., Rensselaer Polytechnic Institute, Troy, New York
Regulation of Blood Glucose Based on Subcutaneous Measurements

4:55 PM Athanassios Sambanis, Ph.D., Georgia Institute of Technology, Atlanta, Georgia
Tissue Engineering a Pancreatic Substitute: Cell Sources and Enabling Technologies

5:15 PM Panel Discussion and Question & Answer

5:35 PM End of Session

5:45-7:45 PM Reception Embassy Hall
Poster Presentations

7:45-9:45 PM Posters Remain on Display for Viewing

Agenda • Saturday, November 2, 2002

7:00 AM Registration Embassy Hall

7:00 AM Continental Breakfast Embassy Hall

Session III - Alternate Routes of Insulin Delivery

8:00 AM Welcome International Ballroom
David C. Klonoff, M.D., University of California, San Francisco

8:05 AM Moderator
Richard Furlanetto, M.D., Ph.D.,
Juvenile Diabetes Research Foundation International, New York, New York

8:10 AM Beth Laube, M.D., John Hopkins University, Baltimore, Maryland
Treating Diabetes with Aerosolized Insulin

8:30 AM William Landschulz, M.D., Ph.D., Pfizer Inc, Groton, Connecticut
Inhaled Insulin (ExuberaTM) Clinical Update

8:50 AM Viren Sarin, Ph.D., Eli Lilly and Company, Indianapolis, Indiana
Relating the Physicochemical Properties of Insulin to Drug Delivery

9:10 AM Jerry Palmer, M.D., University of Washington, Seattle, Washington
Are Insulin Antibodies Induced by Therapeutic Insulin Important?

9:30 AM Panel Discussion and Question & Answer

9:50 AM Break — Embassy Hall

10:30 AM Moderator
Dorian Liepmann, Ph.D., University of California, Berkeley

10:35 AM J. Gordon Still, M.D., Ph. D., Nobex Corporation, Research Triangle Park, North Carolina
An Orally-Active Modified Insulin: Potential for Therapeutic Success in Treatment of Patients with Type 1 and Type 2 Diabetes Mellitus

10:55 AM Richard Guy, Ph.D., University of Geneva, Switzerland
Transdermal Insulin Delivery - Separating Fact from Fiction

11:15 AM Lutz Heinemann, Ph.D., Profil Institut for Metabolic Research, Neuss, Germany
Time-Action Profile of a New Rapid Acting Inhaled Insulin with High Biopotency

11:35 AM Alfred Mann, MannKind Corporation, Sylmar, California
Business Trends in the Diabetes Technology Industry

11:55 AM Panel Discussion and Question & Answer

12:15 PM Lunch — Centennial I

Session IV - Computers and Diabetes

1:30 PM Moderator — International Ballroom
Neal Pellis, Ph.D., NASA Johnson Space Center, Houston, Texas

1:35 PM Ronald Merrell, M.D., F.A.C.S., Virginia Commonwealth University, Richmond, Virginia
Current Status of Telemedicine Technology: Potential Applications to the Management of Diabetes

1:55 PM Riccardo Bellazzi, Ph.D., University of Pavia, Italy
Telematic Management of Diabetes: Current European Experiences

2:15 PM Karsten Jungheim, German Diabetes Research Institute, Duesseldorf, Germany
How Rapid does Glucose Concentration Change in Daily-Life of Patients with Type 1 Diabetes?

2:35 PM Panel Discussion and Question & Answer

2:50 PM Moderator
Judith Fradkin, M.D., National Institutes of Health, Bethesda, Maryland

2:55 PM Lawrence Blonde, M.D., Ochsner Clinic, New Orleans, Louisiana
The Use of Blood Glucose Information

3:15 PM David Horwitz, M.D., Ph.D., LifeScan, Inc., Milpitas, California
Innovations in Data Management in Diabetes

3:35 PM Peter Scanlon, M.D., Cheltenham General Hospital, Cheltenham, England
Telemedicine in Diabetic Retinopathy Screening

3:55 PM Panel Discussion and Question & Answer

4:10 PM Break Embassy Hall

Session V - Demonstrations of Continuous Glucose Monitoring Technology

4:40 PM Moderator International Ballroom
Gerold Grodsky, Ph.D., University of California, San Francisco

4:45 PM Bruno Reihl, Ph.D., Disetronic Medical Systems, Burgdorf, Switzerland
Realtime Glucose Monitoring with GlucOnline: Part 1

4:55 PM Steve Gutman, M.D., M.B.A., U.S. Food and Drug Administration, Rockville, Maryland
FDA's Regulation of Glucose Testing Devices

5:15 PM Bruce Bode, M.D., Atlanta Diabetes Associates, Atlanta, Georgia and
Howard Wolpert, M.D., Joslin Diabetes Center, Boston, Massachusetts
Extemporaneous Interpretation of Freshly Downloaded Data from the Medtronic MiniMed Continuous Glucose Monitoring System

5:40 PM Bruno Reihl, Ph.D., Disetronic Medical Systems, Burgdorf, Switzerland
Realtime Glucose Monitoring with GlucOnline: Part 2

5:50 PM Panel Discussion and Question & Answer

6:10 PM End of Session

Summaries

Clinical Measurement of Long Term Glycemic Control in Diabetic Patients

Garth E. Austin, M.D, Ph.D.

Atlanta VA Medical Center/Emory University
Department of Pathology and Laboratory Medicine (113)
1670 Clairmont Road, Decatur, GA 30033
Tel: (404) 235-3006 • Fax: (404) 235-3007
gaustin@emory.edu

Hemoglobin and other proteins, because of their constant exposure to solutions containing sugar, undergo a process called glycation, that is the nonenzymic addition of sugar residues to certain of their amino groups. Protein glycation proceeds in two steps. First, glucose interacts with the protein by a rapid, reversible process to form an aldimine (Schiff base). The aldimine then slowly undergoes an irreversible Amadori rearrangement to form a ketoamine, which is the product measured clinically. The rate of glycation of any protein molecule is proportional to the average concentration of glucose to which that protein is exposed over its lifetime and hence, the total glycation of a protein is determined by the lifetime of that protein and the time-averaged glucose concentration in its environment.

The first glycated protein to be extensively characterized and utilized clinically for monitoring glucose control in diabetic patients was hemoglobin A1c. Since hemoglobin in red cells is stable and since normal red blood cells have an average life span of about 120 days, hemoglobin A1c values represent the integrated blood glucose value for the preceding 6 to 8 weeks prior to the determination. Studies such as The Diabetes Control and Complications Trial (DCCT) showed that determination of hemoglobin A1c is an effective means for monitoring effects of therapy upon long term glucose levels and that reductions in A1c levels correlate with reduced rates of development of microvascular complications of diabetes. Hemoglobin A1c has been assayed in Clinical Laboratories by a variety of technologies, the most precise of which is high-performance liquid chromatography. The National Glycohemoglobin Standardization Program has been established to standardize glycohemoglobin results obtained by different assays and certify their traceability to values reported in the DCCT.

The relatively long half-life of hemoglobin makes it comparatively insensitive to rapid changes in blood glucose, such as might be seen in labile diabetics during the first few weeks of therapy. For this reason and because, until recently, most hemoglobin A1c assays were labor-intensive and time-consuming, assays of glycation of serum (or plasma) proteins, which turn over much more rapidly than hemoglobin, have had some use in evaluating glucose control. Frucosamine assays (fructosamine is the generic name for plasma protein ketoamines formed by the interaction of glucose with lysine residues on plasma proteins) have been employed in Europe and other parts of the world for many years, but are less popular in this country. Since albumin (whose half life is about 20 days) is the most abundant plasma protein, and since most other plasma proteins have shorter half-lives, frucosamine assays provide a measure of glycation over a time period of one to three weeks. Glycated albumin assays measure the time-averaged glucose levels over approximately the last two-to-three prior prior to the date of the test. Recently developed assays for glycated albumin employ methodologies such as affinity chromatography using monoclonal antibodies which react specifically with glycated albumin. Although these assays are not yet widely employed, their high specificity may lead to an increase in their use.

Recently, point of care assays for hemoglobin A1c and for fructosamine have been developed and have received appropriate FDA approval (and in the case of the A1c assay, NGSP cerification). These assays will be discussed briefly. Most excitingly, non-invasive methodologies for hemoglobin A1c determination are also in advanced stages of development by several companies, and seem likely to be approved for clinical use within the near future.

We are in an exciting time with regard to assays of intermediate and long term diabetic control. Clarification of the relative roles of point of care testing versus in-laboratory testing in diabetic management and of the effectiveness of non-invasive methods of A1c determination will be but two of the important tasks which will face us in the immediate future.

Telematic Management of Diabetes: Current European Experiences

Riccardo Bellazzi, Ph.D.

Universita di Pavia
Dipartimento di Informatica e Sistemistica
via Ferrata 1, Pavia, Italy 27100
Tel: 39 038 250 5511 • Fax: 39 038 250 5373
riccardo.bellazzi@unipv.it

The recent advances of Information and Communication Technologies (IT) have transformed telemedicine into a mature field, so that the research results collected over years can be nowadays translated into clinical practice. Diabetes management represents a sort of natural field for the application of new distributed model of care, that fully exploits currently available telemedicine solutions. For example, the US Health Care Financing Administration (HCFA) has recently funded the IDEATel project with a $28 million grant; IDEATel is the largest telemedicine effort ever funded by the US federal government. Also in Europe there are several projects that are testing innovative IT-based services for supporting diabetes management. Within the V framework research programme of the European Commission, about 40 projects have been devoted to home-care telemedicine applications: 8 of them dealt with the application of IT to the management of Diabetes. Some of those projects were targeted on testing specific technological solutions, such as ADICOL or MOEBIUS, while some other have been oriented to cope with specific aspects of the disease, such as TOSCA, which dealt with diabetic retinopathy. The M2DM project (Multi-Access Services for Managing Diabetes Mellitus patients) was devoted to design and test a platform for managing all type of Diabetic patients. The basic concept of M2DM is to collect data in a central database server that can be accessed through the Web, through the phone or through dedicated software for data downloading from the glucometers. The basic technical service includes a Web access, a Computer telephony integration service based on an Interactive Voice response system and a smart-modem located at home. The Web pages are optimised for different access modalities, including the Web-TV. A distinguishing feature of M2DM is to exploit technology for managing the knowledge available to patients and physicians. To this end, the information flows is regulated by a scheduler, called Organizer, that, on the basis of the knowledge on the health-care organization, is able to automatically send e-mails and alerts notifications as well as to commit activities to software agents, such as data analysis. Four medical centres and 80 patients in three European countries are involved in a randomised controlled evaluation. The evaluation will include five different outcome classes, including clinical, organizational, economical, quality of life and usability dimensions. The talk will be divided into two parts: in the first part, it will be given an introduction on the current status of the European research on telemedicine applications in Diabetes care; in the second part, it will be presented the M2DM project, together with the some results obtained in its clinical evaluation.

Regulation of Blood Glucose Based on Subcutaneous Measurements

B. Wayne Bequette

Rensselaer Polytechnic Institute
Department of Chemical Engineering
110 Eighth Street, Troy, NY 12208-3590
Tel: (518) 276-6683 • Fax: (518) 276-4030

The automated regulation of blood glucose requires a glucose sensor, an insulin pump and a "control algorithm" to adjust the insulin infusion rate in response to the sensor output. Many continuous glucose sensors are based on subcutaneous or interstitial fluid measurements. We discuss how a model can be used to estimate blood glucose values based on subcutaneous measurements. We also present an approach that estimates a disturbance (meal consumption) and adjusts the insulin infusion in response to the disturbance.

In our model predictive control approach, a computationally efficient model is used to predict blood glucose concentrations over a future (prediction) horizon. An optimization algorithm calculates the sequence of current and future insulin infusion rates that will maintain blood glucose near desired values. Each time that a new subcutaneous glucose concentration measurement is available, a Kalman filter is used to estimate the blood glucose concentration. This estimation algorithm provides an optimal trade-off between measurement noise, model and input uncertainty. This model-based approach also estimates unknown meal disturbances, although the diabetic can enter an assumed meal intake to achieve better blood glucose regulation.

In this simulation-based study a high-order compartmental model is used to represent the diabetic patient, but a low-order model is used for the estimation and control algorithms. We discuss how to formulate the estimated disturbance in the context of a Kalman filter, and how to tune the estimation and control algorithms to handle various levels of sensor noise and model uncertainty.

The Use of Blood Glucose Information

Lawrence Blonde, M.D.

Ochsner Clinic Foundation
Brent House 629
1514 Jefferson Highway, New Orleans, LA 70121
Tel: (504) 842-4096 • Fax: (504) 842-3327
lblonde@Ochsner.org

Optimal modern therapy of both Type 1 and Type 2 diabetes uses a "treat to target" approach, expeditiously moving patients along a sequence of therapies to optimize glycemic control. To make effective and efficient decisions about therapy, patients and health care professionals should rely on appropriate information, of which self monitored blood glucose (SMBG) data is a key component. A treat to target approach requires the adjustment of antidiabetic medications, food, and exercise in response to SMBG results.

Few would argue that optimal glucose control would be difficult to achieve without the data generated from a blood glucose meter, especially for patients who use insulin. However, the data generated from blood glucose meters, especially for those who test frequently, are often difficult to interpret. This session will focus on the effective use of blood glucose information for making clinical decisions to improve diabetes control.

The session will review some of the scientific basis for the utilization of a treat-to-target approach in patients with diabetes and the evidence for the benefit of glucose monitoring in patients with both type 1 and type 2 diabetes. It will present solution-oriented approaches to the challenges that health care professionals face in their attempts to use blood glucose monitoring data most effectively.

Clinical Issues in Calibrating Sensors

Bruce Buckingham, M.D.

Lucile Packard Children's Health Services
Pediatric Endocrinology & Diabetes
Stanford University
Room 'S-302, Medical Center, Stanford, CA 94305-5208
Tel: (650) 723-5791 • Fax: (650) 856-8998
buckingham@stanford.edu

Until a factory calibrated continuous glucose sensor (CGS) is available, current sensors are calibrated to the individual, and multiple calibrations are generally entered to improve sensor accuracy. These calibrations are made against home glucose meters (HGM) which have significant variability in there accuracy and precision and are subject to user error. The American Diabetes Association (ADA) has recommended that home blood glucose meters should have a total error of <10% (1). In a recent article assessing the accuracy of adults in performing blood glucose monitoring, patients performed two unassisted measurements using their own glucose meter (2). Five meters were tested. The percentage of measurements that deviated from the laboratory glucose value by >10% was 48%, 43%, 43%, 19%, and 58% for the five meters. In a study of pediatric patients, only 19% washed their hands and of these only 15% waited for their hands to dry before testing, and 30% failed to put the cap back on the strip container which could affect subsequent results (3).

The inaccuracies of a HGM can effect CGS performance. One measure of meter or sensor accuracy is the mean absolute relative difference (MARD) of the measured glucose to reference methods for measuring glucose. In studies performed at Cygnus, the MARD between the One Touchâ Profileâ meter and the Yellow Springs Glucose Analyzer (YSI) was 8.8%. When the Cygnus GlucoWatch Biographer® was calibrated against a YSI analyzer the MARD for the Biographer was 17.4%, but when the Biographer was calibrated against a One Touch Profile the MARD was 21.3%.

Another source of inaccuracies are patient errors in correctly entering the meter glucose values into the CGS. The Medtronic Minimed® CGMS is calibrated by the user entering at least three blood glucose values from a HGM each day. We reviewed the data stored in HGMs with the values entered into the CGS during 19 uses of the CGS in 11 subjects. In 14, HGM data were entered into CGS by the parents; in 2 by an adolescent; and in 3, both the adolescent and parent entered data. There were at least 4 paired readings in the CGS each day with an average of 6.3/d. We found several types of errors: 1) data entered late (>15 min delay), 2) wrong glucose value entered (varied from the HGM value by >10%), 3) HGM values entered twice, and 4) HGM values were obtained but not entered into the CGS.

	Delayed entry	Wrong value	Entered twice	Not entered
# of HGM readings	20	8	11	80
% of CGS entries	5	2	3	21

Overall 10% of the HGM values were entered with errors that could compromise the accuracy of CGS values, and over 20% of values obtained by HGM were not entered into the CGS which, if entered, would improve accuracy of the CGS.

To overcome these types of errors, we suggest: 1) the software of the CGS be modified to allow correction of the glucose values entered into the CGS, or 2) there could be an automatic download of meter values into the CGS software, or 3) a home glucose meter could be incorporated into the CGMS so that glucose values will be directly entered into the CGMS system.

1. Association AD. Self-Monitoring of Blood Glucose. Diabetes Care 1996;19, Suppl. 1:S62-S66.
2. Skeie S, Thue G, Nerhus K, Sandberg S. Instruments for self-monitoring of blood glucose: comparisons of testing quality achieved by patients and a technician. Clin Chem 2002;48:994-1003.
3. Perwien AR, Johnson SB, Dymtrow D, Silverstein J. Blood glucose monitoring skills in children with Type I diabetes. Clin Pediatr (Phila) 2000;39:351-7.

A Novel Continuous Glucose Monitoring System Based on Impedance Spectroscopy: the Calibration Procedure

A. Caduff[1], E. Hirt[1], R. Dewarrat[1], L. Heinemann[2], Yu. Feldman[1]

[1]Pendragon Medical
Hagenholzstr, 81A
Zurich, Switzerland, CH-8050
Tel: +41 43-299 60 10 • Fax: +41 43-299 60 11
andreas.caduff@pendragonmedical.com

[2]Profil GmbH, Neuss, Germanny

The first minimal-invasive continuous glucose monitoring systems are available now. However, there is still a great interest to develop a truly non-invasive glucose monitoring system because this ideally should allow checking the metabolic control over long periods of time without the necessity to breach the skin.

We are developing a novel non-invasive continuous glucose monitoring system, which is based on impedance spectroscopy. In contrast to the different optical approaches studied so far, impedance spectroscopy measures how changes in blood composition affect the impedance pattern of the human skin and underlying tissue. The sensor system has the size of a wristwatch, holding an open resonant circuit coupled to the skin, performing the impedance measurement. By varying frequencies in the radio band over a certain range, optimised to measure the impact of glucose on the impedance pattern, changes in blood glucose (BG) can be monitored indirectly. A one-hour run-in period is required after mounting the sensor in order to reach the equilibrium between skin and the sensor.

Measured impedance changes are temperature corrected, as variations in temperature have an impact on the impedance. These impedance measurements are then transformed into a glucose concentration.

Interpersonal differences like different thicknesses of the skin layers and underlying tissue and their electrical characteristics require an initial two-point calibration.

The calibration procedure provides information about the absolute offset and the ratio between impedance changes and glucose changes.

In summary, this system allows a continuous glucose monitoring with a truly non-invasive approach after an individual two-point calibration procedure.

The SMSI Continuous Glucose Sensing System

Anthony W. Czarnik, CSO

Sensors for Medicine and Science, Inc.
12321 Middlebrook Road, Suite 210, Germantown, MD 20874
Tel: (301) 515-7260 • Fax: (301)-515-0988
awczarnik@s4ms.com

Sensors for Medicine and Science, Inc. (SMSI) is developing and commercializing a new, broadly enabling optical sensing technology. This patented technology permits highly sensitive detection and measurement of molecules of significant commercial interest to the medical, industrial and environmental industries. We have used this technology to develop a miniature (size of a Tic-Tac) implantable sensor that contains an inductively powered (i.e., wireless) optical and electronic platform integrated with a glucose sensing fluorescent indicator immobilized into a glucose polymer. The fluorescence-based non-consumptive glucose indicator and the inductive powering of the implanted sensor is anticipated to allow long-term (12 months after implantation) functioning of the sensor. The information on glucose levels will be communicated to a small wearable external unit. The external unit will display current and historical values, and will have hyper- and hypoglycemic alarm settings and lifestyle event markers.

Calibration of Glucose Measurements Made in Transdermal Body Fluid Accessed via Micropores in the Stratum Corneum of the Skin

Mark Faupel, Ph.D

SpectRx, Inc.
6025A Unity Drive, Norcross, GA 30071
Tel: (770) 242-8723 x303 • Fax: (770) 242-7075
mfaupel@spectrx.com

Several studies have shown that interstitial fluid (ISF) can be a reliable surrogate for blood in the measurement of physiological glucose. In most cases, implantable sensors that are in direct contact with ISF in the dermis are used and can be subject to encapsulation by platelets and other immune system processes that alter the response of the sensor over time, requiring multiple recalibrations per day. The potential advantage of the present system (SpectRx,

Inc., Norcross, GA) is that there are no implanted components, as the body fluid is collected through the stratum corneum via micopores. Because the sensor is not in as hostile environment as implanted sensors, it should be more stable, assuming response to glucose is repeatable both within and between sensors. We summarize five studies using two approaches that utilize SpectRx's method of creating micropores with a focused laser beam and then continuously harvesting plasma-like transdermal body fluid (TBF) for two days using small amounts of vacuum pressure.

In the first system, a continuous stream of TBF is drawn over a proprietary assay contained in a disposable collection device affixed to the skin. The output of the assay is an electrical current that varies continuously as a function of glucose concentration and is read by a dedicated meter that contains both the vacuum source and electronics. Calibration of the assay requires an initial or daily blood fingerstick. Prototypes of this system have recently been evaluated in three populations: 56 diabetic adults (aged 18-79), 60 elderly diabetic subjects (aged > 60 years) and 60 diabetic children (aged 4 to 17). Results from the first study, involving 1264 glucose data points, indicated that 94.1% of the continuously collected TBF glucose data was in the Clarke A&B zones when calibrated once daily and referenced to blood fingerstick glucose (Precision QID, Abbott Labs, Abbott Park, IL). When low sensitivity sensors were calibrated twice daily (about 25% of sensors), the percentage of continuously collected TBF glucose data in the Clarke A and B zones increased to 97.7%. The latter two studies have recently been completed and are undergoing analysis.

In an alternative system, TBF also was collected by microporation and vacuum, but instead of using a dedicated pump and meter system "tethered" by a wiring and tubing set to the disposable assay patch, TBF was collected in a reservoir and measured using a commercially available blood glucose strip. The advantages of this system are that there are no custom electronics that are tethered to the disposable patch and no fingerstick blood needed for calibration. In two studies, one using an electric vacuum pump with a hollow tube connected to the TBF collection device (n = 187 adult diabetic and 65 adult non-diabetic subjects; 4059 data points) and one using a small, untethered mechanical vacuum pump integrated into the TBF collection device (n = 20 elderly diabetic subjects; 124 data points), over 99% of the uncalibrated TBF glucose measurements were in the Clarke A and B zones when referenced to fingerstick blood.

Calibration Considerations for a Three-day Implantable Sensor

Benjamin Feldman, Ph.D.

TheraSense, Inc.
1360 South Loop Road, Alameda, CA 94502
Tel: (510) 749-5420 • Fax: (510) 239-2799
ben.feldman@therasense.com

The TheraSense continuous glucose monitoring system uses a subcutaneous electrochemical sensor, which is implanted for three days. Calibration relies on information gained from both (1) sensor lot pre-implantation testing, and (2) testing of capillary blood samples during sensor implantation. Calibration schemes were evaluated in a clinical setting by comparing the calculated subcutaneous glucose values with reference venous blood glucose values obtained at 15 minute intervals over the entire 3 day implantation period. The efficacies of different calibration schemes are compared.

A Three-day Subcutaneous Glucose Sensor Based on Wired Enzyme™ Technology: Evaluation in People with Diabetes

Benjamin Feldman, Ph.D.

TheraSense, Inc.
1360 South Loop Road, Alameda, CA 94502
Tel: (510) 749-5420 • Fax: (510) 239-2799
ben.feldman@therasense.com

The TheraSense continuous glucose monitoring system uses a subcutaneous electrochemical sensor, which is implanted for three days. A Wired EnzymeTM sensing element transduces subcutaneous glucose concentration to an electrical current. Additional membrane layers serve to (1) increase signal stability, (2) improve the linearity of the glucose-derived signal, and (3) increase the biocompatibility of the implanted sensor.

Subcutaneous blood glucose measurements are presented for diabetic subjects, and are compared to reference venous blood glucose values obtained at 15 minute intervals over the entire 3 day implantation period. Data are presented for implant sites in both the arm and abdomen, including data from simultaneous implantation of dual sensors in both the arm and abdomen.

The Implantable Glucose Sensor: What's "Easy" and What's Not

David Gough, Ph.D.

University of California, San Diego, Department of Bioengineering
9500 Gilman Drive, La Jolla, CA 92093-0412
Tel: (858) 822-3446 • Fax: (858) 822-3467
dgough@bioeng.ucsd.edu

Development of an implantable glucose sensor has been a goal of many investigators for more than three decades and remains an important need in diabetes therapy. The main advantage of an implanted sensor over other types of sensors is that it makes direct contact with bodily fluids and can employ immobilized glucose oxidase as the specific glucose recognition agent. One such sensor based on electrochemical oxygen detection coupled to the immobilized enzyme reaction and configured as a central venous implant has been reported to function over 400 days in humans. Certain other sensors may also be nearing clinical introduction. Now that there is considerable experience with various sensor principles, fabrication approaches and validation methods, an assessment can be made of the remaining technical challenges and their relative difficulties. This assessment should include such issues as the specificity for glucose, sensor stability and recalibration, implant compatibility with the biological environment, dynamic response, signal processing, implantation and replacement methods, methods of sensor system validation, implant safety, and design for user acceptability. The assessment should be based on the general performance requirements of all glucose monitoring systems, such as accuracy, the ability to follow typical glycemic excursions, and the reliability of timely hypoglycemia detection.

FDA's Regulation of Glucose Testing Devices

Steven Gutman, M.D.

U.S. Food and Drug Administration
Division of Clinical Laboratory Devices
2098 Gaither Road, Rockville, MD 20850
Tel: (301) 594-3084 • Fax: (301) 827-4595
sig@cdrh.fda.gov

FDA began regulating medical devices in 1976 with passage of the Medical Device Amendments. Premarket review of glucose measurement devices is based on intended use and technology. Standard laboratory instruments for measuring glucose and home-use blood glucose meters are regulated through the premarket notification or 510(k) program. This requires a demonstration of substantial equivalence to predicate devices and is based on an assessment of device accuracy or bias, precision, and analytical specificity and sensitiity. FDA has recently participated actively in development of an international standard for self-monitoring blood glucose meters developed by the ISO TC 212 committee for international standardization. This document outlines minimum requirements for determination of meter performance and provides a common ground for device comparisons. Non-invasive or minimally invasive monitors, which use alternative and less well established matrices, are regulated through the premarket approval application (PMA) program. They require a de novo demonstration of safety and effectivenss for the claimed intended uses. FDA has worked hard to improve its scientific review process. The agency uses standard regression techniques, clinical tools such as the Clarke Error Grid model, and data stratification models to evaluate new technologies. The agency is charged with maintaining least burdensome pathways to ensure rapid transfer of new technology from research to clinical use. We encourage manufacturers to interact with our regulatory scientists early and often in the course of product development and to submit protocols for review prior to clinical studies. Collaborative scientific discussions lead to better data collection and product labeling, can reduce premarket review time, and as a result can have a profound positive impact on public health.

Transdermal Insulin Delivery– Separating Fact From Fiction

Richard H. Guy, Ph.D.

Universite' de Geneve, Section de Pharmacie
30, quai Ernest Ansermet, Geneva 4, Switzerland, CH-1211
Tel: 33 450 31 50 21 • Fax: 33 4 50 95 28 32
richard.guy@pharm.unige.ch

While transdermal drug delivery has enjoyed considerable commercial success, the technology has thus far been limited to low molecular weight agents (e.g., nitroglycerin, estradiol, nicotine). The passive skin transport of molecules of greater than 1000 daltons, including insulin, of course, is severely limited by the remarkably impermeable structure of the stratum corneum, the outermost and least permeable layer of the membrane. Much effort has therefore been directed towards methodologies to increase the permeability of the skin, either by the application

of an additional force (over and above the concentration gradient) to the drug of interest, or by lowering the diffusional resistance of the barrier. In the former category, iontophoresis has achieved, at best, sporadic results but has nevertheless been well-studied; in the latter case, diverse approaches have been examined, ranging from the use of chemical enhancers and the formulation of complex vehicles, to electroporation, sonophoresis and a spectrum of so-called minimally invasive techniques (e.g., microneedles, microperforation techniques, and so on). The aim of this presentation is to review the state-of-the-art, with respect to the transdermal delivery of insulin, and to separate fact and reality from fantasy and fiction.

Funded in part by the Fonds national suisse de la recherche scientifique, and the Programme commun en Génie Biomédicale (Universities of Geneva and Lausanne, and the Ecole Polytechnique Fédérale de Lausanne).

Calibration and Continuous Glucose Monitoring: An Elusive Goal?

Lutz Heinemann, Ph.D.

Profil Institut for Metabolic Research
Hellersbergstr. 9, Neuss, Germany 41460
Tel: 49 2131 4018 402 • Fax: 49 2131 4018 502
lutz.heinemann@profil-research.de

Correlating glucose values as they are measured by a glucose sensor in the interstitial fluid to blood glucose values appears to be quite simple. Only take a blood glucose meter, measure the glucose level in a freshly collected blood drop, use the result for a correction factor of the result of a parallel measurement with the glucose sensor. Users, physicians and the respective authorities believe that this all they have to know about the calibration procedure of glucose sensors; and they believe that the procedure and the need for calibration is more or less identical for all different types of sensor. However, in reality the calibration procedure involves several pitfalls and sources of trouble and there are massive differences between the various sensors with respect to the calibration requirements.
First of all, it is important to be aware of the fundamental difference between spot blood glucose measurement and continuous glucose monitoring, especially with a focus on the calibration process: Blood glucose meters usually are calibrated by the manufacturer. With glucose sensors, however, the customer himself has to calibrate the sensor system, with some systems even several times a day! It is a clinical problem that every error in the calibration procedure will propagate into all subsequent measurements, until the next calibration.
One aspect that make the calibration procedure problematic, beside a considerable number of others, is that most glucose sensors that are on the market (or are in clinical development) measure glucose changes in the interstitial fluid and not directly in the blood. Up to now, the degree of correlation between glucose changes in the blood and the interstitial fluid in humans is not sufficiently studied in terms of temporal and absolute relationship. Currently, there is no glucose sensor on the market in the US which has the approval for therapeutic decisions by patients with diabetes based on the measured results. One of the main reasons for such restrictions by the authorities is the problematic calibration process. Should the sensor system measurement show glucose values that indicate the need for intervention, these ought to be confirmed by conventional measurements. Of course, in everyday life patients will tend to ignore such restrictions.

In summary, the importance of the calibration procedure and its proper handling must be made very clear to the patients. Many details of this procedure remained to be studied in detail.

The Joint DOD / NASA / NIH / JDRF Technologies for Metabolic Monitoring (TMM) Program

Michael Hopmeier, M.S.M.E.[1], Col. John F. Glenn, Ph.D.[2], Robert Goldstein, M.D., Ph. D.[3], John Hines, M.S.E.E.[4], LTC Karl Freidl, Ph.D.[2], Kim Hunter-Schaedle, Ph.D.[3], Maren Laughlin, Ph.D.[5], Murray Loew, Ph.D.[6], David Klonoff, M.D.[7]

[1]Unconventional Concepts, Inc.
Washington, D.C.
hopmeier@unconventional-inc.com
[2]US Army Medical Research and Materiel Command, Fort Detrick, Maryland
[3]Juvenile Diabetes Research Foundation International, New York, New York
[4]NASA Ames Research Center, Moffett Field, California
[5]National Institutes of Health, Bethesda, Maryland
[6]George Washington University, Washington D.C.
[7]Mills-Peninsula Health Services, San Mateo, California

The Technologies for Metabolic Monitoring Program (TMM) is a joint initiative of the U.S. Army Medical Research and Materiel Command (MRMC), the Juvenile Diabetes Research Foundation (JDRF), NASA, and NIH (NIDDK). It was initiated and is directly sponsored by Congress and has been chiefly supported by Congressman George Nethercutt. TMM's focus is provide support and assistance in the identification and maturation of potential new, novel, and innovative technologies for the monitoring and assessment of metabolism, but especially as those may apply to the care and long-term health maintenance of the diabetic.

The goal of the effort has defined the rather unusual mix of sponsors, federal and nongovernmental, and, on the face of it, extremely diverse. The key focus of the effort, however, is to improve the understanding, and tools to exploit that understanding, of metabolism. TMM is, in the truest sense of the word, a "dual-use technology". As it will, when successful, it provides for the underpinnings of the ability to not only improve the performance of a wide array of personnel in physically and mentally demanding tasks (ranging from soldiers to astronauts to air traffic controllers and long-haul truckers). TMM also offers the opportunity to better understand, and control, diseases of the metabolism such as diabetes. For that reason, these four organizations have combined to bring this effort forward and support a variety of researchers in this demanding and critical field.

Innovations in Data Management in Diabetes

David L. Horwitz, M.D., Ph.D.

LifeScan, Inc.
1000 Gibraltar Drive, Milpitas, CA 95025
Tel: (408) 956-4885 • Fax: (408) 941-9895
dhorwitz@lfsus.jnj.com

The increasing use of intensified therapy in diabetes, calling for multiple insulin injections guided by frequent determination of blood glucose, allows the collection of large amounts of data reflecting the effectiveness of glycemic control. A patient injecting insulin four times a day, and testing four times a day, will generate over 240 data points a month from glucose and insulin data alone. When data on food intake, intercurrent illnesses, periodic evaluations such as HbA1c, and events such as hypoglycemic episodes are added to the data base, the amount of data available becomes difficult to use when manual review of patient diaries is the only tool used. Yet proper use of this data base offers the possibility of recognition of patterns of glucose excursions, determination of optimal insulin doses for various meals and times of day, and explanations of departures from the usual state of control.

Modern data processing and storage technology offers the potential for summarization and display of large amounts of data in a form that may facilitate use of the data to monitor diabetes management. In one implementation of this, the OneTouch UltraSmart® blood glucose monitoring system, this data storage and display function has been incorporated into the glucose meter. Suggested uses of the system will be presented.

New Technology for Improving Access to Immediate A1C Results

Benjamin R. Irvin, Carole R. Stivers, Annette L. Clark, Joel M. Blatt, and Erika B. Ammirati[1]

Metrika, Inc.
510 Oakmeade Parkway, Sunnyvale, CA 94085
Tel: (408) 524-2255 • Fax: (408) 524-2252
birvin@metrika.com

[1]Ammirati Regulatory Consultants, Los Altos, CA

As the A1C assay becomes standardized through the efforts of the NGSP, its utility as the primary status indicator is enhanced in the diabetes treatment and management community. Several studies have provided evidence of improved outcomes for patients whose A1C results were obtained and communicated at the point-of-care. Current technology for immediate A1C results ranges from full-scale laboratory analyzers for clinics with very high patient volumes to the A1cNowTM single-use A1C monitor.

The A1cNow Monitor is the result of six years of development on a miniaturized, single-use platform for point-of-care (POC) diagnostics. With the use of custom integrated circuits, molded micro-optics, and high-volume electronic manufacturing techniques, a four-channel precision reflectometer can be economically built in a single-use device. Reflectance standard deviations are typically below 0.1%. About the size of a pager, an A1cNow Monitor is extremely portable and adaptable to a variety of healthcare environments.

The A1cNow assay begins with a fingerstick blood sample diluted into a provided vial of treatment buffer. The only input from the user is addition of the diluted blood. The %HbA1c value is determined by combining a competitive immunoassay result for the HbA1c component and methemoglobin reflectance for total hemoglobin. Both assays develop in a microporous membrane substrate run in duplicate. A1cNow was certified by the NGSP in June 2002 and is therefore traceable to the methods used in the DCCT for measuring glycated hemoglobin.

In two recent clinical trials performed to support application for OTC clearance, over 200 patients were given A1cNow Monitors to run on their own with no training beyond the included packaging and labeling. In addition, a second test was performed on each patient by a healthcare professional. Venipuncture samples were sent to an NGSP Secondary Reference Laboratory. The combined results of these studies showed that both patients and experienced professionals were equally able to use the test and obtain equivalent valid results. The mean bias (vs. NGSP lab) for patient-performed results was 0.06 while that for professionals was 0.09 %HbA1c. The 95% confidence interval for individual result bias from the reference value was ?0.96 to 1.08 %HbA1c for the patients and -0.78 to 0.96 %HbA1c for the professionals. These in-field results compare well with the NGSP interval requirement of ±1 %HbA1c for certification of both methods and Level II laboratories.

A clinical utility study was performed at Atlanta Diabetes Associates involving 60 patients (one day). Each patient had an A1C test done with the A1cNow and with the clinic's standard method, the Bio-Rad Variant II. The correlation between the methods was 0.94 with a regression line slope of 1.03. The mean bias between A1cNow and the Variant II was +0.15 %HbA1c. Health care providers in the clinic found 98% of the A1cNow results to be useful for patient management.

Clinical Pathologist's View of Continuous Glucose Sensor Calibration

Frederick L. Kiechle, MD, Ph.D

William Beaumont Hospital, Dept. of Clinical Pathology
3601 W. 13 Mile Road, Royal Oak, MI 48073
Tel: (248) 551-8020 • Fax: (248) 551-3694
fkiechle@beaumont.edu

The continuous measurement of glucose using the FDA approved Minimed Continuous Glucose Monitoring System (MiniMed, Inc., Sylmar, CA) or GlucoWatch Biographer (Cygmes, Inc, Redwood City, CA) for a subset of difficult to control insulin-treated diabetics in a hospital is very appealing in the face of a shortage of medical technologists and nurses to perform point-of-care fingerstick glucose measurements. However, the current continuous measurement devices (whole blood or plasma-based) are dependent on capillary glucose values for calibration. "Calibration is the process of testing and adjusting an instrument, kit or test system to provide a known relationship between the measurement response and the value of the substance that is being measured by the test procedure." (CLIA-88:493-1217) The current continuous glucose calibration methods are subject to potential errors introduced by the portable glucose meter, or the lag time between the blood glucose concentration and interstitial fluid value. Improvements in continuous glucose meter calibration include an internal calibration system which would also detect potential substances interfering with the direct oxidation of electroactive species at the amperometric sensors, inflammation at the implantation site and/or protein coating the sensor surface.

Treating Diabetes With Aerosolized Insulin

Beth L. Laube, Ph.D.

John Hopkins Hospital, Park 316
600 North Wolfe Street, Baltimore, MD 21287-2533
Tel: (410) 502-5791 • Fax: (410) 955-1030
blaube@jhmi.edu

Diabetes is a disease that affects approximately 16 million people in the U.S. A large number of this population will require insulin treatment at some point in their lives. Because injection of insulin is associated with pain and a disruption of lifestyle, patient compliance with this treatment regimen is often compromised, leading to potentially suboptimal treatment outcomes. There is no pain with aerosol therapy, so it is not surprising that a number of investigators have examined the possibility of administering aerosolized insulin as an alternative to injection.

In the 1970s and 1980s, several groups of investigators showed that insulin aerosol was absorbed through the respiratory epithelium of patients with diabetes and was biologically active, since plasma insulin levels increased and glucose levels decreased, respectively (1-2). Building on this information in the early 1990s, other investigators combined new knowledge about dose and aerosol delivery and successfully normalized fasting glucose levels in patients with diabetes by delivering aerosolized insulin through the lungs (3). Using a similar approach in a later study, these investigators found that the intrapulmonary delivery of aerosolized insulin was also effective in lowering glucose levels after a meal (4).

Although these early studies demonstrated the feasibility of treating diabetes with insulin aerosol, several issues need to be addressed before intrapulmonary delivery of insulin becomes an alternative to delivery by injection. These include:

- Optimizing the aerosol delivery system
- Assessing the acute and chronic safety of insulin delivered by this route
- Maximizing the relative bioavailability of inhaled insulin

Research into the possibility of treating diabetes with aerosolized insulin has led a number of investigators to consider treating other diseases by intrapulmonary delivery of therapeutic proteins. Like insulin, successful treatment outcomes with other peptides and proteins will hinge on the determination of the correct dosage and formulation for aerosolized delivery of each agent, as well as the development of devices for optimizing delivery within the lung.

References

1.Elliott RB, Edgar BW, Pilcher CC, Quested C, McMaster J. Parenteral absorption of insulin from the lung in diabetic children. Aus Paediatr J 1987;23:293-297.

2.Wigley FW, Londono JH, Wood SH, Shipp JC, Waldman RH. Insulin across respiratory mucosae by aerosol delivery. Diabetes 1971;20:552-556.

3.Laube BL, Georgopoulos A, Adams GK III. Preliminary study of the efficacy of insulin aerosol delivered by oral inhalation in diabetic patients. JAMA 1993;269:2106-2109.

4.Laube BL, Benedict GW, Dobs AS. The lung as an alternative route of delivery for insulin in controlling postprandial glucose levels in patients with diabetes. Chest 1998;114:1734-1739.

New Assessment Criteria for Continuous Glucose Monitoring

Volker Lodwig, Ph.D.

Roche Diagnostics
Sandhofer Strasse 116
D-68305
Mannheim, Germany
volker.lodwig@roche.com

Up to now, patients (and physicians) base their therapeutical decisions on a current result of a spot blood glucose measurement (SBGM). A deviation of the "real" blood glucose value from the measured spot value can have severe clinical consequences. Novel glucose sensors allow a continuous glucose monitoring (CM) over prolonged periods of time. However, we are still used to the criteria which are employed to evaluate the quality of SBGMs. The question now is whether these criteria are also valid for the evaluation of CM.

As there are no standard assessment criteria for CM upon which the academic world and the pharmaceutical industry have agreed, every researcher/every company frequently uses his/her own criteria. This, of course, hampers the comparability of trial results, and it allows to use criteria which favor one particular sensor system. Such assessment criteria are, for example: system error, percent press, MAD (original), MAD (Medtronic MiniMed), Pearson Correlation coefficient. The clinical relevance of parallel measurements frequently is analysed by means of the error grid analysis (EGA). Assessment criteria are usually used for a retrospective evaluation of the quality of obtained data. In order to be of clinical relevance the results of CM clearly have to be displayed on-line. The influence of the calibration process on the data quality then has to be assessed by fixed assessment criteria.

The application of different assessment criteria to data which have been obtained during clinical studies with the Accu-Chek Monitor system currently under clinical development by Roche Diagnostics revealed that none of these criteria allowed a satisfying description of these data. Therefore, we suggest to develop and evaluate novel assessment criteria that will allow such a description. Ideally, all "players" in this area of research should use such standardized criteria in order to allow for a comparability of results and data obtained with the wide range of different CM systems.

Business Trends in the Diabetes Technology Industry

Alfred E. Mann

MannKind Corporation
12744 San Fernando Road, Sylmar, CA 91342-3278
Tel: (818) 362-6266 • Fax: (818) 362-4556
al.mann@mannkind.com

Pulmonary delivery of insulin is an attractive alternative to s.c. insulin injection in the treatment of diabetes mellitus. Several developments are currently under clinical investigation to achieve market approval (Heinemann et al., 2001). TechnosphereÔ (Pharmaceutical Discovery Corporation, Danbury, CT, USA) is a new drug delivery system which captures and stabilizes peptides in small particles. A well characterized small organic molecule, 3,6-bis(N-fumaryl-N-(n-Butyl)amino-2,5-diketopiperazine (FDKP), self-assembles in a mild acid environment into microspheres with a mean diameter of about two microns. In the process it traps and micro-encapsulates any peptide present in the solution during self-assembly. Once dried, these particles become a suitable vehicle for pulmonary delivery to systemic circulation. When administered by the pulmonary route, Technospheres™ dissolve in the pH neutral environment of the deep lung and facilitate the rapid and efficient absorption of the peptide into systemic circulation. The carrier molecules are excreted un-metabolized as ammonium salts in the urine within hours after administration. Extensive clinical work using TechnospheresTM to apply insulin, PTH, glucagon and other drugs has already demonstrated the efficacy, reliability and tolerability of this drug delivery system. (Lian et al, 2000; Mohnike et al., 2000; Pfützner et al., 2002; Pohl et al., 2000; Rave et al., 2000; Steiner et al., 2002). Technosphere™/insulin delivered to Type 2 patients, utilizing the MedTone® inhaler, reaches peak blood levels in about 13 minutes and has a bio-availability of between 40-50% in the first three hours.

We will present our approach to the treatment of Type 2 diabetes using this technology.

Current Status of Telemedicine Technology: Potential Applications to the Management of Diabetes

Ronald C. Merrell, M.D.

VCU Dept. of Surgery
1200 East Broad Street, West Hospital, P.O. Box 980645, Richmond, VA 23298
Tel: (804) 828-7874 • Fax: (804) 827-1016
ronald.merrell@vcu.edu

Telemedicine implies the use of telecommunications to support delivery of health care. The technology of telecommunications has greatly outpaced application in the management of medicine. Therefore, opportunities abound to integrate health care in an information continuum across distance with the expectation of greater access, greater

efficiency and greater accuracy. The elements of successful telemedicine management include accurate collection of data in digital format, incorporation of those data into an electronic record which may be transmitted with fidelity, protocols for distant analysis and communication tools to permit effective dialogue among primary managers, patients and consultants. Seamless management of surgery, anesthesia and highly complex consultation has been achieved. The application of telemedicine to disease management is being broadly considered. In this situation telemedicine does not connect distant health care facilities but embraces the home and daily life of patients for early recognition of problems and timely correction. In diabetes management one must maintain the history and database on a server fed with data for glucose, retinal status alerts for hypoglycemia and mental status change, diet, weight and exercise. The data can be reviewed at intervals for general management as is done with traditional treatment. However, treatment takes on new horizons with the use of home sensors, wireless monitoring, alert notification and interaction from a management center. It is incumbent upon those devoted to improvement in the care of diabetes to examine the available and emerging technology to design and apply appropriate systems of telemedicine. Systems should be compatible with office practice and the life style of patients and must not be prohibitively expensive

Update on the Clinical Progress of a Non-Invasive Blood Glucose Monitor

Stephen L. Monfre, Ph.D.

Sensys Medical, Inc.
7470 West Chandler Blvd., Chandler, AZ 85226
Tel: (480) 755-9483 • Fax: (480) 755-9832
smonfre@imetricsinc.com

Previously we reported progress on the development of a non-invasive blood glucose monitor based on near-infrared diffuse reflectance spectroscopy. Those results validated the technology in a clinical setting using a research grade device and independent test data. Since that time, we have made significant progress on the development of a commercial version of the monitor. The movement of the device from the clinical setting into the hands of consumers carry its own set of concerns which must be dealt with through device design and training, to achieve a smaller, more acceptable form factor of the monitor.

Currently we have interim results from a multi-center study involving over 30 subjects suffering from diabetes. These results are based on the standardized calibration methodology we reported previously, using a device that is approximately 50% smaller than the previous research grade device. To date we have seen a decrease in our mean absolute percent error from ~23% to 18%. Clarke Error Grid analysis has yielded: 81.7% in (A); 18.3% in (B); 0.0% in (C), (D) and (E).

This research represents an investigation into the complexity of the NIR-based, non-invasive methodology and a discussion of potential solutions for reducing the complexity of the device for use by consumers. Factors influencing the reliability of the non-invasive glucose measurement system are discussed and solutions for improving long-term performance are proposed.

Are Insulin Antibodies Induced by Therapeutic Insulin Important?

Jerry Palmer, M.D.

VA Puget Sound Health Care System, Endocrinology (111)
1660 S. Columbian Way, Seattle, WA 98108
Tel: (206) 764-2495 • Fax: (206) 764-2693
jpp@u.washington.edu

Insulin antibodies develop in most patients treated with therapeutic insulin. In my talk I will discuss several factors known to be important in controlling this antibody response and how some currently experimental insulin formulations and modes of administration would be expected to affect insulin antibody production. I will also discuss the data pertaining to the metabolic effects of insulin antibodies on insulin absorption, insulin pharmcodynamics, insulin dose and hypoglycemia. Insulin is an important antigen in the Type 1 diabetes disease process and the antibody response to insulin may reflect an effect of therapeutic insulin on this disease process. In addition, the insulin autoimmune syndrome will be mentioned. Data from animal models and humans with Type 1 diabetes investigating this effect of insulin will also be presented.

In-vivo Glucose Sensing: Clinical Practice and Research

John C. Pickup

Metabolic Unit, Guy's, King's and St Thomas School of Medicine
Guy's Hospital, London SE1 9RT, UK
Tel: 44 207 955 5000 x3014 • Fax: 44 207 403 9810
john.pickup@kcl.ac.uk

Many technologies in diabetes medicine have been slow to enter widespread clinical practice and gain complete acceptance by physicians and patients. Examples include continuous subcutaneous insulin infusion, blood glucose self monitoring and glycated hemoglobin testing, which have all taken more than 20 years to approach clinical maturity. Some of the factors which delay progress include identifying and solving problems in everyday use; proving effectiveness with randomised controlled trials, cost effectiveness and quality of life studies; defining clinical indications and contraindications, and agreeing guidelines for good practice; securing funding for research and for clinical application; and the education of healthcare professionals, governments and patients about the uses and abuses of such technologies. We must learn, too, that technologies must evolve and there is seldom only one technology appropriate for a clinical problem.

Can we learn from the past and accelerate the development of in vivo glucose sensors? Implanted amperometric enzyme electrodes are already 20 years into their application in humans. Three sensors - an enzyme electrode, a reverse iontophoresis and a microdialysis system have recently been commercialised. First trials indicate great clinical potential, some problems and an urgent need to understand the information value of the sensor readings. Most importantly, technologies for non-invasive sensing are still required.

Fluorescence is an example of a technology for glucose sensing which is relatively new and has several advantages for such non-invasive monitoring, particularly with the measurement of lifetimes which are sensitive, independent of light scattering in the tissues and of fluorophore concentration. Fluorophores that can be excited and emit in the near-infrared (NIR) range enable interrogation of sensors from outside the body. The main approaches we are taking include optimisation of a system based on the reduction in fluorescence resonance energy transfer (FRET) between the lectin concanavalin A, labelled with the highly NIR-fluorescent protein allophycocyanin, and dextran-labelled with malachite green, when dextran binding is displaced by glucose. This might be suitable for subcutaneous implantation. An improved sensor measurand that we have introduced is based on determination of donor-acceptor distance distribution functions for FRET in macromolecules, plotting the nm tomography of competitive binding assays. We are also investigating cellular metabolic sensing by both intrinsic fluorescence and reporter molecules, both of which signal glucose-dependent metabolism in the model system of in vitro cell culture.

Critical Issues in the Calibration of a System Sensing Glucose in Interstitial Fluid

Gérard Reach

Hopital Avicenne
125 rue de Stalingrad, Bobiguy, France F93000
Tel: 33 1-48-95-51-58 • Fax: 33 1-48-95-55-60
gerard.reach@avc.ap-hop-paris.fr

The calibration of a glucose sensing system consists first in the determination of the parameters describing the relationship between the sensor output and the concomitant blood glucose concentration, i.e. the sensor sensitivity and the theoretical background current generated in vivo by the sensor in the absence of glucose, and secondly in the subsequent use of these parameters to transform the sensor output into an estimation of glucose concentration.

These parameters can be determined either on the basis of a single blood glucose measurement (one-point calibration), assuming that Io is negligible, or known and constant, or of two measurements (two-point calibration), or even on the basis of all the determinations performed during a calendar day, this last method being however not compatible with on line blood glucose monitoring.

However, an incorrect estimation of Io can first result from a non linear response of the current to a change in blood glucose concentration. Since the sensor monitors interstitial, and not blood, glucose concentration, this lack of linearity can be observed under two circumstances : 1) the sensor response (the increment in the sensor output) to the increase in glucose concentration is really not linear; 2) during an increase in blood glucose concentration, the increase in interstitial glucose concentration is blunted, due for instance to the effect of insulin on glucose uptake from interstitial fluid to the surrounding cells. In this case, the apparent absence of linearity between the increase in the sensor output and blood glucose concentration is situated not at the sensor level, but at the level of glucose transfer from blood to interstitial tissue where glucose concentration is sensed. A second possible cause for a non negligible Io is due to a measurement error on the current and/or the capillary blood glucose measurement during the achievement of the two-point calibration procedure, which has indeed the disadvantage of using two estimations of glucose concentration and sensor output, each adding to the measurement errors.

Prevention of Hypoglycemia Using Risk Assessment with a Continuous Glucose Monitoring System

Gérard Reach[1], Carine Choleau[1], Petr Dokladal[2], Jean-Claude Klein[2], W. Kenneth Ward[3], George S. Wilson[4]

[1]INSERM U341, Diabetes department, Hôtel-Dieu Hospital, Paris, France
[2]Center of Mathematical Morphology, Armines, Fontainebleau, France
[3]iSense, Portland, Oregon
[4]Department of Chemistry, University of Kansas, Lawrence, Kansas

Due to the lag between sugar intake and the beginning of recovery from hypoglycemia, it is necessary to intervene in an anticipatory way if one wants to prevent, and not only to detect, hypoglycemia. This paper presents the principle of a hypoglycemia prevention system based on risk assessment. The risk situation can be defined as the moment when the system estimates that glucose concentration is expected to reach a hypoglycemia threshold in less than a given time (e.g. 20 minutes). Since there are well known discrepancies between blood and interstitial glucose concentration, the aim of this experimental study performed in non-diabetic rats was first to validate this strategy, and second to determine whether it can work when glucose concentration is estimated by a glucose sensor in subcutaneous tissue rather than in blood. We used a model of controlled decrease in blood glucose concentration. A glucose infusion, the profile of which mimicked the appearance of glucose from an intragastric load, was administered either when hypoglycemia was detected, or on the basis of risk recognition. In spite of the lag between the beginning of the load and that of the increase in blood glucose concentration, which was in all experiments 15 - 20 min, hypoglycemia was fully prevented without overshoot hyperglycemia in the groups of rats where the glucose load was started when the hypoglycemia risk was detected, either on the basis of blood, or of interstitial, glucose concentration.

Such was of course not the case when the same glucose load was infused at the detection of the hypoglycemia threshold.

Various Approaches for Closed-Loop Insulin Delivery

Kerstin Rebrin, M.D., Ph.D.

Medtronic MiniMed
18000 Devonshire Street, Northridge, CA 91325-1219
Tel: (818) 576-4156 • Fax: (818) 576-6206
KerstinR@Minimed.com

The common goal of any closed-loop insulin delivery system is to emulate glucose control of healthy individuals as closely as possible. This means keeping glucose values within the normal range with a minimum of insulin delivery. A physiological insulin delivery algorithm is proposed that emulates a normal B-cell response to glucose. Still, the

algorithm has to be adjusted for measuring delays and insulin absorption kinetics depending on the glucose measuring and the insulin infusion site. Advantages and challenges of glucose sensing and insulin delivery at various sites (subcutaneous, intravenous and intraperitoneal) for a closed-loop algorithm will be discussed with regard to optimal algorithm tuning. Data obtained with external and/or implantable Medtronic MiniMed glucose sensing and insulin

delivering devices will be presented as part of closed-loop systems in development for ambulatory and hospital use.

Realtime Glucose Monitoring with GlucOnline

Bruno Reihl

Diesetronic Medical Systems
Brunnmattstr. 6, 3401 Burgdorf, Switzerland
Tel: 41 34 424 2868 • Fax: 41 34 424 2919
bruno.reihl@disetronic.ch

We present our continuous glucose monitoring system "GlucOnline" in a live demonstration. GlucOnline is based on a microdialysis-type fluidic system with a double-lumen dialysis needle to be placed in the subcutaneous tissue by the patient. A highly viscous solution of dextrane and concanavalin A, which is being pumped through the fluidic system, picks up glucose molecules through a membrane which is part of the dialysis needle. The viscosity of the solution decreases with an increasing glucose concentration and may be determined by pressure-difference measurements. Details of the sensor principle are explained in reference 1.

In contrast to dialysis systems for glucose monitoring that utilize an enzymatic sensor in the downstream tube, GlucOnline is not suffering from an inherent time delay, as it is based on a measurement of pressures which are isotropic within the whole fluidic system. Calibration is needed only in the beginning of a measurement, afterwards GlucOnline will display a stable signal of absolute and realtime glucose values, as will be demonstrated by a comparison to conventional fingerprick measurements. It appears feasible that GlucOnline may be used by a patient for up to five days without re-calibration. The agreement between GlucOnline data and conventional blood glucose measurements has recently been investigated in two clinical trials and found to be very good. These results will be discussed along with the live demonstation.

1) U. Beyer et al., Diabetologia 44, 416 (2001).

Calibration Procedures for Subcutaneous Glucose Monitors

Bruno Reihl, Ph.D. and Thomas Vering, Ph.D.

Diesetronic Medical Systems
Brunnmattstr. 6, 3401 Burgdorf, Switzerland
Tel: 41 34 424 2868 • Fax: 41 34 424 2919
bruno.reihl@disetronic.ch

We present hands-on experience with the calibration of different subcutaneous glucose monitors with respect to a) the number of calibrations points needed; b) the time-delay between capillary-blood vs. interstitial-fluid measurements, c) technology-inherent time-delays, d) arm vs. abdominal measurements, and e) the suitability for closed-loop applications. From our clinical-trial results we can deduce first educational measures for patients that will self-apply their glucose monitors with respect to handling and calibration.

Tissue Engineering a Pancreatic Substitute: Cell Sources and Enabling Technologies

Athanassios Sambanis, Ph.D.

Georgia Institute of Technology
School of Chemical and Biomedical Engineering
315 Ferst Drive, IBB Building 1306, Atlanta, GA 30332
Tel: (404) 894-2869 • Fax: (404) 894-2291
athanassios.sambanis@che.gatech.edu

A pancreatic tissue substitute for treatment of insulin-dependent diabetes has significant potential in providing, less invasively, a more physiologic regulation of blood glucose levels than daily insulin injections. Engineering of tissue substitutes requires developing certain core, enabling technologies, which include: (i) Cell technology, which addresses the development of a cell source appropriate for clinical-scale applications and the expression of desirable cell functions in culture and in the construct pre- and post-implantation. (ii) Construct technology, which focuses on designing, manufacturing, preserving, and characterizing the three-dimensional substitute, so that it is functional in vitro and in vivo. (iii) Technologies for in vivo integration, which address issues of biocompatibility, immune acceptance, in vivo efficacy, remodeling and monitoring, and the ability to retrieve or replace the implant, if necessary. This presentation will review our studies on developing these enabling technologies for two distinct systems: (i) continuous insulinoma lines encapsulated for immune protection; and (ii) non-beta cells genetically engineered for insulin secretion in response to physiologic stimuli.

Current Activities at CDC's National Diabetes Laboratory

Eric J. Sampson, Ph.D.

Center for Disease Control and Prevention
4770 Buford Hwy., NE, MS-F20, Atlanta, GA 30341-3724
Tel: (770) 488-7950 • Fax: (770) 488-4839
ejs1@cdc.gov

Scientists at the CDC's National Diabetes Laboratory are collaborating with researchers and national and international organizations worldwide to develop new methods and advanced technologies aimed at preventing and treating type 1 diabetes. Eight major projects are currently under way. Through a variety of activities, the laboratory is working to improve blood glucose measurements made using portable monitoring systems. Scientists are also working with CDC grantees to develop new tools for detecting and monitoring low levels of blood glucose among people with diabetes; others have focused on improving the clinical measurement of hemoglobin A1c and advanced glycation end products. CDC scientists are also collaborating on prevention research for type 1 diabetes through a newborn screening pilot program; developing and ensuring the quality of rapid, highly sensitive methods for measuring markers of type 1 diabetes; improving autoantibody measurements through a rigorous standardization program known as DASP; and testing and banking samples for a major study to determine genetic risk factors for diabetes and its complications. Ultimately, these endeavors will improve the lives of people with diabetes.

Relating the Physicochemical Properties of Insulin to Drug Delivery

Michael R. Defelippis and Viren K. Sarin[1]

[1]speaker
Lilly Research Laboatories
Lilly Corporate Center, MD3848, Indianapolis, IN 46285
Tel: (317) 276-6027 • Fax: (317) 277-0833
defelippis_michael_r@lilly.com

Insulin is known to exist in different self-associated states. At a very low concentration (<0.1 mM), it exists as a monomer. In the absence of divalent metal ions, insulin exhibits a complex association pattern consisting of monomer, dimmer, tetramer, hexamer and high-order forms, all in dynamic equilibrium further influenced by concentration, pH, ionic strength, and temperature. Divalent metal ions such as zinc shift the equilibrium towards hexamers. The association state of insulin has significant implications on physical and chemical stability and in-vivo absorption kinetics. Therefore, understanding the factors modulating insulin association is important in developing dosage forms for various routes of administration (e.g., injectable, pulmonary, oral, buccal, etc.). Similarly, there are a number of known "hot spots" in insulin susceptible to chemical denaturation that have significant implications with respect to formulation and processing parameters. In this presentation, we describe the physical and chemical attributes of insulin and their relationship to its solubility, stability, and in vivo absorption properties.

Telemedicine in Diabetic Retinopathy Screening

Peter Scanlon, M.D.

Cheltenham General Hospital, Dept. of Opthalmology
Sandford Road, Cheltenham Glos, England, United Kingdom GL52 6RH
Tel: 44 1242 274419 • Fax: 44 1242 274420
peter@p5sca.demon.co.uk

Gloucestershire is a county in the UK that has offered digital photographic screening to 12,000 diabetic patients every 2 years since 1998, including those already under ophthalmological care. The attendance rate has been 74%. Results will be presented from the Gloucestershire Diabetic Eye Study, which included 3611 diabetic patients from 56 practices who had two digital photographs taken of each eye, using a Topcon TRNW5s with a Sony 3-chip video camera. This was followed by slit lamp bio-microscopy by an experienced ophthalmologist in 1549 patients. Results from two other Gloucestershire studies will be presented, including one that was designed to assess the impact of JPEG compression of these images and the second to assess the most useful photographic markers for detection of referable maculopathy.
Funding for Diabetic Retinopathy Screening Programmes has been announced in Scotland and in Wales and is expected in England and Northern Ireland. The technology is changing at such a rapid pace that studies designed to assess the latest technology are becoming out of date before completion. Suggestions as to how this problem might be addressed will be given.

An Orally-Active Modified Insulin: Potential for Therapeutic Success in Treatment of Patients with Type 1 and Type 2 Diabetes Mellitus

J. Gordon Still, M.D., Ph.D.

Nobex Corporation
Research Triangle Park, North Carolina
Tel: (919) 474-0507 • Fax: (919) 474-9407
jgstill@nobexcorp.com

Protein and peptide drugs are rapidly degraded in the enteric environment, making them generally unsuitable for oral administration in their native forms. Attempts to improve enteric absorption of proteins using formulations that limit enzymatic degradation and promote absorption have met with limited success. One novel technology is centered on modification of peptides, proteins and small organic molecules by attachment of one or more amphiphilic (balanced water and lipid solubility) oligomers to specific sites on the molecule. Attachment of these oligomers results in stability to enzymatic degradation, improved solubility allowing formulation in absorption-enhancing media, and modification of pharmacologic properties to prolong circulating half-life and biologic activity. This technology has been applied successfully to human recombinant insulin, resulting in creation of an orally absorbed, bioactive conjugate, hexyl insulin monoconjugate 2 (HIM2), which is safe and rapidly absorbed and which demonstrates dose-

dependent, glucose-lowering effects in animal models, healthy volunteers and diabetic patients. Orally administered HIM2 is delivered first to the liver through the portal circulation, similar to the physiological route of insulin secretion in non-diabetics. Potential benefits from this route of insulin delivery include improved glycemic management with reductions in hypoglycemic events, overall improvement in diabetes related health outcomes, reductions in progression of type 2 diabetes, and reduction of long-term complications of type 1 and type 2 diabetes. Results of recently completed studies evaluating both single and multiple short-term dosing in both type 1 and type 2 diabetic patients suggest a promising role for conjugated insulin in the management of post-prandial hyperglycemia. Further studies using longer-term dosing of HIM2 are planned to investigate the potential benefits of HIM2 in treatment of both type 1 and type 2 diabetic patients.

Diabetes Research in Children Network (DirecNet): Testing Sensor Technology in Youth with Type 1 Diabetes

William V. Tamborlane, M.D.

Yale School of Medicine, Department of Pediatrics
P.O. Box 208064, 333 Ceder Street, New Haven, CT 06520
Tel: (203) 785-4646 • Fax: (203) 737-1998
william.tamborlane@yale.edu

Results of the Diabetes Control and Complications Trial (DCCT) indicate that most patients with T1DM should be treated intensively in order to reduce the risk of progression of retinopathy and the development of microalbuminuria. Translation of DCCT recommendations for treatment of youth with T1DM was anticipated to be especially challenging, since adolescents in that study had both higher HbA1c levels and an increased risk for severe hypoglycemia compared to adults. However, the recent introduction of continuous glucose monitoring systems has provided pediatric practitioners with new tools to meet the special challenges presented by treatment of T1DM in youth. In this presentation we will review published data regarding the use of glucose sensors in young patients with T1DM. In addition, we will discuss the organizational structure of the newly formed, NIH-sponsored Diabetes Research in Children Network (DirecNet), a consortium of 5 academic pediatric diabetes centers whose aim is to test the clinical utility of continuous glucose monitoring in children. Ongoing studies and future plans of the Network will be reviewed.

Calibration of Subcutaneous Glucose Sensing

Bill Van Antwerp[1], Todd Gross, John Mastrototaro, Udo Hoss

[1]Medtronic MiniMed
18000 Devonshire St., Northridge, CA 91325
Tel: (818) 576-4913 • Fax: (818) 576-6250
bill.van-antwerp@minimed.com

Calibration of subcutaneous glucose sensors is a difficult task. A patient typically will use a finger stick or alternate site discrete glucose measurement to generate a calibration data point. This presents two difficulties. The main difficulty is that the subcutaneous compartment has potentially significant time delays with respect to the blood compartment. This means that the blood value that is used to calibrate the sensor is almost certainly different from the tissue value that is being measured by the sensor. The second issue is that there are almost certain errors in the discrete blood value itself, leading to inaccurate calibration. In this study, we present data from a simulation study where the relationship between the blood and tissue glucose levels is not fixed. We choose a variety of calibration points and describe the resulting tissue glucose estimation statistics, the blood glucose estimation statistics and finally we explore the differences between single and multiple point calibrations.

Abstracts

(A1-A139)

Estimation of the Diabetic Children's Condition with the Help of the Computer Programme «DiabCare Q-Net»

G. Ahmedov, A. Halikova

Azerbaijan Medical University, Baku, Azerbaijan
azdiabet@hotmail.com

Diabetes type 1 is a disease caused by absolute or relative insulin deficiency in organism, which is associated with the disturbances of carbohydrates metabolism or with impairment of other metabolic processes. Insulin therapy is used in diabetes. Thus, if the treatment is wrong, the complications may occur. This may result in pathologic changes of other organs.

The aim of this investigation is to estimate the children's conditio ns in diabetes. To achier the aims the following duties must be carried out.
1. The investigation of the sick children's physical condition.
2. The investigation of the most frequent complications in patients.
3. The investigation of the patients, which take insulin injection.

The objects of the research work were 65 children with diabetes type 1. 42,0(6,16% of them were the girls, 58,0(6,16% the boys. The average age of these children was 10,6(0,42 years old. The duration of the disease was 3,3(0,31 year. The estimate the diabetic children's condition a special computer programme «DiabCare Q-Net» have been used. This investigations is a part of the computer programme. The diabetic children have been considered according to the physical development the weight and height. According to these features 55,6(6,21% of the patients were with normal weight, 19,1(4,91% of the patients were with abnormal weight and height, 20,6(5,05% of the patients were with normal weight, lagging height, 4,7(2,64% were with normal height, weight was lagging.

Proteinuria had been revealed in 30,9(5,77% of patients. Microalbuminuria occurred in 24,4(5,37% of patients. Microalbuminuria is the first sign of nephropathy in diabetes. The chronic complications of diabetes cataract had been occurred in 7,4(3,27% of patients. Neuropathy had been revealed in 33,8(5,91% patients. Other complication of diabetes ketoacidosis had been revealed in 22,2(5,19% of patients. HbA1 shows the period of disease remission, 8%- HbA1 had been determined in 13(4,20% of patients, 8-9,5% HbA1- in 5(2,72% of patients, over 9,5% HbA1- in 82,0(4,80% of patients. This shows the patient`s decompensation condition. 11,2(3,94% of patients are those which take 2-3 times insulin injection, 77,6(5,21% of patients 4-6 times a day.

So using computer «DiabCare Q-Net» programme gives the possibility to observe and estimation the condition of diabetic children every year.

Computers in the Delivery of Diabetes Care

AM Albisser, PhD

Professor and Director, Diabetes Disease Management Systems
BCMC Better Control Medical Computers, Inc
1413 20th Street Unit 207, Miami Beach FL 33139
Phone: (305) 534-9970 • Fax: (305) 674-1814
albisser@nidm.org

Background. This presentation contrasts changes in outcomes resulting from three initiatives of diabetes care delivery: (i)education alone, (ii)education with added self-management training and, (iii)education with informatics-supported self-care. Outcomes of interest were changes in glycated hemoglobin (HbA1c), body weight and costs of care.

Methods. Patients with diabetes were included in the 3 initiatives for improving blood glucose control. HbA1c was measured at baseline, 3 and 12 months, body weight at baseline and 12 months. Costs of care per month were calculated. Costs were derived from suppliers and the billings to health plans of the subjects. A longitudinal observation study design was used.

Results. With the education-alone initiative, costs, HbA1c and body weight were unchanged. In the initiative that included education enriched with on-going self-management training(Staged Diabetes Careä), HbA1c fell 1.1% ($p<0.01$), but body weight rose by 11kg($p<0.01$) and costs for care increased by $618 per patient per month. In the initiative that included education enhanced with computer-assisted self-care(HumaLinkä), HbA1c also dropped by 1.1% ($p<0.01$), body weight was unchanged($p>0.4$) and costs for care increased by $45 per patient per month.
Conclusions. Efforts to improve care delivery in diabetes beyond those currently achieved by education alone appear possible. Self-management training can enrich education but it is labor intensive and risks increasing body weight. Computer-assisted glucose control is effective, more than an order of magnitude less costly, and appears capable of avoiding body weight gain. Computer supported care breaks with tradition. It emulates an industrial approach which automates physician monitoring, patient reporting and coordinates interventions aimed at improving outcomes. Since this method involves centralized infra-structure, it reduces face-to-face encounters and delivers benefits while realizing significant economies of scale.

A Bayesian Approach to Bergman's Minimal Model

Dr. Kim Emil Andersen[1], Dr. Malene Højbjerre[2]

[1]Department of Mathematical Sciences
Aalborg University
Fredrik Bajers Vej 7G
DK-9220 Aalborg East
Tel.: +45 96358849 • Fax: +45 98158129
emil@math.auc.uk

[2]Department of Mathematical Sciences
Aalborg University
Fredrik Bajers Vej 7G
DK-9220 Aalborg East
Tel.: +45 96358925 • Fax: +45 98158129
malene@math.auc.dk

The classical minimal model of glucose disposal (Bergman et al., 1979) was proposed as a powerful modeling approach to estimating the insulin sensitivity (SI) and the glucose effectiveness (SG), which are very useful in the classification, prognosis and therapy of diabetes. The minimal model is based on a standard frequently sampled intravenous glucose tolerance test (IVGTT), which consists in administering a single intravenous injection of glucose over a small period of time and then measuring the resulting glucose and insulin concentrations in plasma.

The minimal model is a highly ill posed inverse problem and most often the reconstruction of the glucose kinetics has been done by deterministic iterative numerical algorithms. However, these algorithms do not consider the severe ill posedness inherent in the minimal model and may only be efficient when a good initial estimate is provided. In this work we adopt graphical models as a powerful and flexible modeling framework for regularizing the problem and thereby allow for the estimation of the insulin sensitivity and glucose effectiveness. We illustrate how the reconstruction algorithm may be efficiently implemented through the use of Markov chain Monte Carlo techniques and demonstrate the method on a real set of field data.

Bergman, R.N., Ider, Y.Z., Bowden, C.R. and Cobelli, C.: Quantitative Estimation of Insulin Sensitivity, American Journal of Physiology, 236 (1979), E667-77.

Diabetes Awareness and Education in an Interactive Science Center

Joseph Andrade, Chair and Executive Director

Utah Science Center @ Library Square
949 Mill Creek Way,
Salt Lake City, UT 84106
Phone: 801-581-4379 • Fax: 801-585-5361
joeandrade@uofu.net
www.utahsciencecenter.org

The rapid growth in diabetes and pre-diabetes syndromes has led to increased interest in activities on diabetes awareness and education, including the National Diabetes Education Program (http://ndep.nih.gov) and the activities of the American Association for Diabetes Education (www.aadenet.org). There is also growing recognition that new and expanded approaches are needed to reach under served and minority populations (Diab. Metab. Res. Rev. 2002; 18: 26; JAMA 2002: 288: 82). There is also growing demand on teachers to facilitate diabetes self management in schools (Diab. Tech. Therap. 2001; 3: 601).

There are major national resources that are underutilized for diabetes awareness and education: interactive, experiential science and technology centers. About 100 million people per year visit the several hundred interactive, science centers in the USA (www.astc.org). The science center environment is objective, experiential, non-threatening, and conducive to new levels of awareness and education. Most science centers tend to avoid medical issues and problems, in part because it is difficult for such topics to meet the hands-on, interactive requirement of most science center exhibits and activities.

The Utah Science Center (USC) will open in early 2004 in Salt Lake City. A major theme of the USC is measurements ON the visitor, that is, the visitor is the subject, the object, the specimen, and the sample in a suite of activities related to health, medicine, life styles, and genetics.

This talk will encourage audience input regarding design and implementation of diabetes-related activities in the new Utah Science Center (www.utahsciencecenter.org).

Non-invasive Ocular Glucose Sensing Apparatus

Rafat R. Ansari[1], Luigi L. Rovati[2], and Stefan Bockle[2]

[1]NASA Glenn Research Center
21000 Brookpark Road, MS 333-1, Cleveland, OH 44135
Tel: (216) 433-5008 • Fax: (216) 977-7138,
rafat.r.ansari@grc.nasa.gov
[2]Department of Information Engineering
University of Modena and Reggio Emilia via Vignolese 905, I-41100, Modena, Italy
Tel: 39-059-205-6111 • Fax: 39-059-205-6126
rovati.luigi@unimo.it

An optoelectronic apparatus for measuring the concentration of glucose in the human body is described. The apparatus can perform polarimetric and interferometric measurements of the human eye to acquire data from which the concentration of glucose in the aqueous humor can be computed. The optical scheme exploits the Brewester reflection of circularly polarized light off the ocular lens. An experimental laboratory set-up based on this scheme was designed and tested by measuring a range of known concentration of glucose solutions.

The Potential Clinical Implications of the Pharmacokinetic Profiles of Insulin Administered by Alternate Routes

Ehud Arbit M.D., Richat Abbas Ph.D., Steve Dinh Ph.D. and Michael Goldberg M.D.

Ehud Arbit MD
V.P. Medical Research
Emisphere Technologies Inc
Professor Cornell University Medical College
New York. NY.
914-785-4702

Several large prospective studies have shown a reduced risk of microvascular and macrovascular complications from diabetes mellitus (DM) with tight glycemic control and lowered hemoglobin A1C thus supporting the strategy of aggressive blood glucose control. There are now about 180 branded insulin preparations available worldwide, but despite this wide and ever increasing array of insulins, replacement of physiological insulin and attainment of tight glycemic control remain elusive goals.

A variety of alternative (non-parentral) routes and methods of insulin administration including the trans- bucchal, trans-nasal oral and pulmonary are under investigation. The PK profiles of some of these newer methods of insulin delivery are characterized by rapid insulin absorption and clearance. The question raised is if and where in the treatment paradigm of the diabetic patient, such a PK profile of insulin may find its role.

Methods: literature review

Discussion: The timing and magnitude of the early-phase insulin response is critical for receptor-mediated insulin action and glucose tolerance. The PK of some of the alternate routes of insulin administration replicate the early-phase insulin response and as such may find a role in a) the restoration of the physiologic pattern of insulin secretion in the early stages of T2DM thereby improving glucose homeostasis. b) as a mean to spare the ß cells in IGT and hence delay or prevent progression to T2DM as in the DPP and STOP-IDDM studies c) to be given before each meal as part of a basal bolus regimen d) to serve as vehicles for the so called fourth generation of protracted insulins that have delayed clearance from the circulation.

The physiologic pattern of insulin secretion, its significance and a comparison to the PK profile of currently used insulins and the emerging insulins will be discussed.

The Blood Glucose Pattern Index: an Algorithm for Detecting and Reporting Patterns in Self-Monitored Blood Glucose Data

Eric Stephen Armbrecht, B.S.[1] (correspondent) and Jonathan Bortz, M.D.[2]

[1]St. Louis University School of Public Health
607 Forest Ct., #203
St. Louis, MO 63105
Tel: 314-277-5162 • Fax: 888-671-6734
eric@icontroldiabetes.com

[2]Jonathan Bortz, M.D.
Control Diabetes Inc.
6520 Clayton Road
St. Louis, MO 63117
Tel: 314-644-6575 • Fax: 314-644-2342
jonathan@coanco.net

Introduction

Primary care physicians (PCPs) are the central providers of diabetes care in the US. Numerous studies document their difficulty with diabetes treatment goals, including glycemic control. Insufficient or inappropriate use of self-monitored blood glucose data for medication management and lifestyle modification contributes to PCPs' difficulties with diabetes management.

A new algorithm called the Blood Glucose Pattern Index (BGPI) streamlines the analysis of blood glucose data. In many ways, the algorithm's output is to diabetes what the interpretive EKG is to cardiology - a diagnostic tool that facilitates clinical decisions.

Methods

The BGPI classifies infinite possibilities of blood glucose reading patterns into finite, clinically meaningful statements about a patient's glycemic control. Three steps through customizable decision rules ascertain different clinically meaningful patterns of blood glucose readings. To ease understanding and use by healthcare providers, decision rules avoid complex statistics and favor graphical representations. Some variables used by the algorithm are: target range, severe hypoglycemia threshold, severe hyperglycemia threshold, percentage of readings in-target / above target / below target, mean value of readings in-target / above target / below target.

Example output from the analysis of pre-prandial blood glucose readings using the BGPI can be viewed in Table 1. Post-prandial data may be analyzed as well.

Discussion

The purpose of the BGPI is to (1) assess a patient's glycemic control and (2) facilitate clinical intervention by an attending healthcare provider. By providing the PCP with a textual assessment of glycemic control, he/she can more readily identify problem areas and prescribe appropriate treatment.

Table 1.: Example Output of the BGPI

Assessment of Patient Jane Doe's glycemic control from 1/1 to 1/30: Before Breakfast: Optimal Control, with isolated severe hypoglycemia Before Lunch: Widely Fluctuant, with a range from 46 to 343 Before Dinner: Frequent Significant Hyperglycemia, with isolated severe hyperglycemia Before Bedtime: Satisfactory Control, with notable hyperglycemia Source: 0% data self-reported; 100% data directly from meter

Ten-Year Coronary Heart Disease Risk in Diabetic Patients

Salim Aziz, M.D.[1], Abdul-Karim Elhabyan, M.D.[2], Bernardo Jose Fernandez, M.D., Mike Broce, B.A., B. Daniel Lucas, Jr., Pharm.D.[3]

[1]HLTxAziz@aol.com - Corresponding Author
[2]abdulkarim.elhabyan@camc.org
[3]Dan.Lucas@camc.org

Diabetes has been listed as a coronary heart disease (CHD) risk equivalent in the most recent NCEP (National Cholesterol Education Program) guidelines. One of the reasons for this classification is the assumption that diabetes confers a similar risk for CHD as patients with existing CHD (i.e., absolute CHD risk >20% per decade). Objective: We estimated soft (angina, nonfatal MI, CHD death) and hard CHD (excludes angina) risks in a diabetic cohort using two of the Framingham risk equations. Methods: One hundred forty-seven non-hospitalized diabetic patients without known CHD were scored for 10-year CHD risks. Besides diabetes, other elements required for scoring included age, total-cholesterol (TC), HDL-C, blood pressure, and smoking status. Results are mean+standard deviation. Results: The cohort's (age 53.2+13.0 years; 70.1% female) 10-year hard and soft CHD risks were 9.6+8.6% and 15.0+10.6%, respectively. Cohort demographics follow: SBP 139.9+19.8mmHg, DBP 82.2+9.8mmHg, BMI 32.9+7.3kg/m2, HDL 44.0+11.5mg/dL, LDL 119.3+35.2mg/dL, TC 203.7+42.0mg/dL, triglycerides 207.4+122.7mg/dL, fasting glucose 146.9+49.3mg/dL, positive CHD family history 37.4%, HTN history 83.7%, and smoking history 7.5%. Conclusion: In this non-hospitalized diabetic cohort, the 10-year absolute hard CHD risk was half the assumed >20% CHD risk. These results lead one to question whether the Framingham risk equations underestimate the CHD risk in diabetic patients or whether the short-term CHD risk assumption for diabetes is incorrect. Results are especially noteworthy in light of the present NCEP treatment algorithm for hyperlipidemia in diabetic patients.

Automated Capture of Patient Monitoring Data

Timothy Bailey, M.D., F.A.C.E., F.A.C.P.

North County Endocrine Medical Group
735 East Ohio Avenue Suite 203
Escondido, CA 92025
(760) 743-1431 x205
tbailey@ucsd.edu

For nine months we have used an Internet-based patient registry for diabetes management called MediCompass®. The system allows our physicians to capture and track relevant data, display it graphically, and screen our patient population for individuals who would benefit from an intervention. A unique feature of the system is automated capture of patient monitoring data, including blood glucose.

Initial experience was with downloading from the patient's glucose meter when the patient arrived at clinic, but now patients can submit the data from home, using a portable device (MetrikLink®) that sends the data to the MediCompass® system by secure dial-up connection (no Internet connection required). Administrative staff enters the remainder of the data.

Patients with Internet-access are encouraged to view their data online using a password-protected patient portal. Patients may enter their medications into the system in advance of their visits; this saves valuable time during the encounter, and helps to keep the registry up-to-date.

The principal value of the system so far has been the capture and graphic display of patient data for individual patient care. As more data is captured over time, the population case management value of the system will come to the forefront, enabling better identification of patients who need care interventions. We are also able to evaluate patients' adherence to their regimens, a critical but difficult metric to obtain from populations with chronic diseases. Evidence-based quality measures can be tracked and reported. Finally, the system facilitates report generation for payers and others who request population data on patients using a unique ethical, private, and secure framework.

Details of our experience will be presented.

American Indian Diabetic Teleophthalmology Grant Program - A Practical Case Study Examining Challenges and Methods for Success

Heather Bernikoff, MS[1] (presenter); Sandy McGrath, RN, MSN[2]

[1]CA Telehealth & Telemedicine Center
1215 K Street, Suite 800
Sacramento, CA 95814
Tel.: 916.552.7687 • Fax: 916.552.7526
hbernikoff@calhealth.org

[2]CA Rural Indian Health Board, Inc.
4400 Auburn Blvd, 2nd Floor
Sacramento, CA 95841
Tel.: 916.929.9761 • Fax: 916. 929.7246
sandy.mcgrath@mail.ihs.gov

In 2000, active planning began on establishing a group of Indian Health Programs with advanced capabilities to screen for diabetic retinopathy among their many diabetic patients. In the Indian community, diabetes is at epidemic proportions, and in 1998, according to Indian Health Service data, only 39% of diabetic patients were receiving their required eye examinations. This low rate is attributed to many variables, the most significant being rural locations where specialists are unavailable, lack of transportation, and cultural discomfort with unknown providers.

Training began for the first of the 13 funded Indian Health Programs in March of 2001. A working product was finally installed, four months later, in July. Many challenges presented themselves in the planning, implementation and current maintenance of this program. Since the first working systems were installed, 277 patients have been screened for diabetic retinopathy using this technology (through May 2002). Retinopathy has been suspected in 17 of these patients.

The usefulness of the system varies from site to site, but, in general, has gone beyond retinopathy screening. It has been a catalyst for increased organizational benefits - such as improved patient education opportunities, establishing relationships between clinic and specialist, and has identified acute conditions, which may have otherwise gone unfound until permanent damage ensued.

In this session, both the challenges and successes of this program will be discussed as well as the latest quantitative and qualitative evaluation data. Special attention will be paid to the human networks necessary for successful integration into the primary care setting. Practical guidelines will also be offered for participants interested in beginning a teleophthalmology program in their venue.

Prediction of Insulin Sensitivity Index Using Bayesian Networks

Susanne G. Bøttcher[1] and Claus Dethlefsen[2] (presenter)

Dept. of Mathematical Sciences
Aalborg University
Fr. Bajers Vej 126
9220 Aalborg East
Denmark
Tel: 9635 8878 • Fax: 9815 8129
[1]alma@math.auc.dk
[2]dethlef@math.auc.dk

A Bayesian network is a graphical model that encodes the joint probability distribution of stochastic variables, which in our case may be continuous and/or discrete. By specifying the dependency structure through a Directed Acyclic Graph (DAG), the joint probability distribution factorizes according to this DAG.

A method for estimating the parameters and learning the dependence structure of networks with mixed variables is presented in Bøttcher (2001). If used on networks with only discrete or continuous variables, it coincides with the methods developed in Heckerman et al. (1995) and Geiger and Heckerman (1994).

We have developed a package, DEAL, written in R, which provides methods for analysing datasets using Bayesian networks, see Bøttcher and Dethlefsen (2002). In particular the package includes procedures for defining priors, estimating parameters, calculating network score, structural learning as well as simulating datasets with a given dependency structure.

The methodology is illustrated by analysing data from a study where the aim is to determine the relationship between the insulin sensitivity index (ISI) and the insulin concentration measured at fixed time points in an oral glucose tolerance test. The ISI was determined from an intraveneous glucose tolerance test. We use a Bayesian regression model expressed as a Bayesian network to estimate parameters in the prediction model.

The work has been supported by Novo Nordisk Ltd.

Use of CGMS in Patients with Type 1 Diabetes treated with CSII and MDI - Clinical Experience

Jan Broz*, Michal Andel

2nd Dep.Int.Med., 3rd Medical Faculty of Charles University
Prague, Czech Republic

*2.int.klin. FNKV
Srobarova 50
Prague, Czech Republic
Tel: 00420267162710 • Fax: 00420267162710
zorb@seznam.cz

Background and aims: We wanted to determine if the use of CGMS in patients with type 1 diabetes treated with CSII or MDI can result in decrease number of symptomatic hypoglycaemias.

Subjects: 14 patients with type 1 diabetes treated with CSII (4 female and 10 men, age 37,2 ± 9,4 year (Mean±SEM), duration of disease 14,5± 7,1 year, duration of treatment 2,6± 1,64 year and 8 patients with type 1 diabetes treated with MDI (4 times a day, 2 female and 6 men, age 34,6± 8,2 year, duration of disease 8,2 ± 4,8 year).

Control group: 11 patients with type 1 diabetes treated with CSII (2 females, 9 males, age 34 ± 8,2 year, duration 12,1± 6,8 year, and 7 patients with type 1 diabetes treated by MDI (2 females and 5 males, age 31 ± 7,1 year).

Methods: symptomatic hypoglycaemic episodes were recorded 16 weeks prior and 16 weeks after monitoring, HbA1c values were obtained in weeks - 8, 0 , +8 and +16. Each patient worn CGMS for 3 working days during his normal avtivity. All patients were also advised to provide all special activities (eg. Sport, sauna,..). Important events including insulin injection, exercise, meals and hypoglycaemic episodes were self recorded. After CMGS use , continuous glucose profiles were reviewed to identify changes in therapy. Therapy adjustment included changes to insulin dosage , diet and treatment of low and high blood glucose values.

Results: Patients treated with CSII: we found a decrease in number of symptomatic hypoglycaemias per month/ patient: 6,69 ± 1,84 (no nocturnal or severe event) vs. 10,2± 3,6 in previous period (7 nocturnal, 1 severe event), $p < 0,05$ (weeks 1-8: 6,58 ± 1,56 hypoglycaemias per month, weeks 9-16: 6,87 ± 1,68). We also found decrease in HbA1c: week 8: 7,1±0,52%, week 16: 7,4±0,58% vs. 7,9±0,59% at baseline, resp. 7,7 ± 0,62% in week -8, ns.

Patients treated with MDI: we found a decrease in number of symptomatic hypoglycaemias per month/patient in weeks 1-8: 8,29 ± 1,76 (1 nocturnal or severe event) vs. 11,4 ± 4,2 in previous period , $p < 0,05$, number of symtpomatic hypoglycaemias in weeks 9-16 remained on the same level. We found a decrease in number of nocturnal hypoglycaemias (week 1-16: 3, vs. week -16-0: 12) We did not find significant improvement in GHBA1c levels.

Control group: we did not find significant changes neither in number of symptomatic hypoglycaemias nor in HbA1c levels in both group.

Conclusion: CGMS provides meaningful data for individuals to personalize their pump insulin regimen to reduce risk of symptomatic hypoglycaemias and keep the level of diabetes compensation and has parcial impact also on patients treated with MDI.

The Joslin Vision Network Picture Archiving and Communication System (PACS) for Eye Health Care

Sven-Erik Bursell, PhD[1]*, Paul R. Conlin, MD[2]*, Mark Horton, OD, MD[3], Robert Vigersky, MD[4], Anthony Cavallerano, OD[5], and Lloyd M. Aiello[6]*

[1]Director, Joslin Vision Network (Correspndent)
Beetham Eye Institute
Joslin Diabetes Center
One Joslin Place, Boston, MA 02215
Phone: 617 732-2583 • Fax: 617 264-2776
Sven.Bursell@joslin.harvard.edu

[2]Chief Endocrinologist,
VA Boston Healthcare System
Division of Endocrinology and Hypertension
221 Longwood Avenue, Boston, MA 02215
Phone: 617 732-5661 • Fax: 617 732-5764
Pconlin@partners.org

[3]Chief, Ophthalmology Service
Phoenix Indian Medical Center
4212 N. 16th Street, Phoenix, AZ 85016
Phone: 602 263-1200 • Fax: 602 263-1635
Mark.horton@pimc.his.gov

[4]Director, Diabetes Institute
Walter Reed Army Medical Center
Washington, DC 20307-5001
Phone: 202 782-5212 • Fax: 202 782-0187
Robert.vigersky@na.amedd.army.mil

[5]Beetham Eye Institute
Joslin Diabetes Center
One Joslin Place, Boston, MA 02215
Phone: 617 732-2588 • Fax: 617 264-2776
Anthony.cavallerano@joslin.harvard.edu

[6]Beetham Eye Institute
Joslin Diabetes Center
One Joslin Place, Boston, MA 02215
Phone: 617 732-2520 • Fax: 617 264-2776
Lloyd.m.aiello@joslin.harvard.edu

The Joslin Vision Network (JVN) optimizes computer and telemedicine technologies to facilitate appropriate eye care for all diabetic patients. The core application is based on non-mydriatic stereoscopic retinal imaging from remote sites with assessment for clinical levels of diabetic retinopathy at the Beetham Eye Institute of the Joslin Diabetes Center and at certified regional reading centers. The expectation is that the JVN can provide cost-effective solutions for accessing all diabetic patients into appropriate eye care.

JVN technology uses commercially-available PCs to run its application in a standards-compliant network for visible light objects and allows integration into existing health information systems. The PACS network permits patient scheduling and capture of relevant medical record information - either automatically, via the host electronic medical record system, or by hand, from the patient's chart at the time of the study.

The application facilitates image capture, display, storage and reader notification. At the reading center, the JVN application provides retrieval and display of these images. The readers enter findings electronically and the JVN rules-based algorithm provides the level of diabetic retinopathy and a treatment plan for referral or follow-up based on risks for progression.

Studies performed to date demonstrate that the JVN non-mydriatic stereoscopic retinal images taken with the JVN system are equivalent to the clinical "gold standards" of dilated retinal stereo photography and dilated examination by a retinal specialist. Other studies have shown that the system frequently provides useful information on other, non-diabetic pathology. The JVN system enhances access for diabetic eye care and increases patient compliance to subsequent eye examinations.

Intrahepatic Immune Events Interfere with Longterm Islet Allograft Acceptance

Ginny L. Bumgardner*, Keri E. Lunsford, and Donghong Gao

Division of Transplantation, Department of Surgery,
Ohio State University Medical Center, Columbus, Ohio 43210.

*Ohio State University Medical Center
Department of Surgery, Division of Transplant
1654 Upham Drive, 373 Means Hall, Columbus, Ohio 43210-1250
Tel: 614-293-6177 • Fax: 614-293-4541
cooper-7@medctr.osu.edu

Despite improvements in clinical intrahepatic islet transplantation, islet allografts remain vulnerable to late allograft failure. One potential cause of late islet allograft failure is activation of donor-reactive immune responses in the local immune environment where islets have engrafted. The purpose of this study was to determine if local immune events in the liver can precipitate failure of established intrahepatic islet allografts. Hepatocyte transplantation was used as a tool to deliver donor-specific alloantigens to the host liver where intrahepatic islets have engrafted. Methods: Diabetic C57BL/6 (H-2b) mice received intrahepatic or intrakidney FVB/N (H-2q) islet transplants. Islet acceptance was achieved with donor-specific transfusion (d-7) and anti-CD40L mAb (d-7,-4,0,4). Glucoses <200mg/dl defined islet function and >250mg/dl defined rejection. Islet acceptors were challenged with intrahepatic injection of either donor-matched (FVB/N) or control syngeneic (C57BL/6) hepatocytes (2x106). Results: When intrakidney islet acceptors were challenged with donor-matched hepatocytes (delivered to the liver), islets continued to function in 3 of 4 mice. In contrast, when intrahepatic islet acceptors were challenged with donor-matched hepatocytes (into the liver), islets were rejected in 3 of 4 mice. Alloantibody, which was suppressed in islet acceptor mice prior to donor-antigen challenge, increased significantly in intrahepatic but not intrakidney islet acceptors after donor-matched HcTx. When intrahepatic islet acceptors were challenged with syngeneic hepatocytes, islets maintained function for >60 days in all recipients. Alloantibody in islet acceptors was negligible prior to and after syngeneic HcTx. Conclusions: These data suggest that local immune events in the liver can adversely influence established islet allografts. Hepatocytes stimulate both independent CD4+ and CD8+ T cell pathways. Future studies will address the specific immunologic pathway(s) precipitating failure of these islet allografts.

Non-invasive, Continuous Glucose Monitoring System based on Impedance Spectroscopy

A. Caduff[1], C. Kapitza[2], E. Hirt[1], R. Dewarrat[1] and L. Heinemann[2]

A. Caduff: andreas.caduff@pendragonmedical.com (corresponding author)
E. Hirt: etienne.hirt@pendragonmedical.com
R. Dewarrat: rodolphe.dewarrat@pendragonmedical.com
[1]Pendragon Medical
Hagenholzstr. 81a, CH-Zurich, Switzerland
Phone: +41 43 299 60 10 Fax: +41 43 299 60 11

C. Kapitza: christoph.kapitza@profil-research.de
L. Heinemann: lutz.heinemann@profil-research.de (presenting author)
[2]Profil Inst. for Metabolic Research
Hellersbergstr. 9, D-41460 Neuss, Germany
Phone: +49 2131 4018400 Fax:+49 2131 4018500

We investigated a novel non-invasive continuous glucose monitoring system, which is based on impedance spectroscopy. In contrast to the different optical approaches studied so far, impedance spectroscopy investigates how changes in blood composition affect the impedance pattern of the human skin and underlying tissue. By varying frequencies in the radio band over a certain range, optimised to measure the impact of glucose on the impedance pattern, changes in blood glucose (BG) can be monitored. However, this indirect method does not allow a specific glucose measurement. As electrolytes in body fluids contribute to the impedance pattern we investigated the relationship between electrolyte concentrations at different BG levels. The sensor used in these experiments has the size of a wristwatch, holding an open resonant circuit coupled to the skin, performing an impedance measurement. In a series of 15 glucose clamps, healthy volunteers were connected to a Biostator, which allows to set BG to predefined target levels. The BG level was increased rapidly from euglycemic to hyperglycemic values (100 to 300 mg/dl, baseline infusion of somatostatin). Electrolyte concentrations were periodically measured (Na+, K+, Ca2+, Cl-, Mg2+) by standard laboratory methods.

10 of 15 experiments showed a good correlation (Clark Error Grid A 52%, B 43%) between changes in BG and the sensor recordings and a good correlation between the BG profile and electrolytes Na+, K+, Cl- was monitored as well.

In summary, we demonstrated with these experimental human studies a clear correlation between changes in BG and the signal obtained with this novel non-invasive monitoring approach.

A Control Oriented Model of Type 1 Diabetic Patients

V Canonico, PG Fabietti, P Ferolla, M Iorio, M Massi Benedetti, M Orsini Federici, E Sarti

DIMI Department of Internal Medicine, University of Perugia, Italy

Aim: A mathematical model of insulin and glucose homeostasis (DTM 2001 poster N°) was used in connection with a clinical test on eight patients. The target was to personalize parameters and investigate the patients response to different events and mainly to a feed-back controlled insulin infusion. Proportional-derivative (PD) control algorithms were tested on the model.

Methods: Eight type 1 diabetic patients on continuous subcutaneous insulin infusion (CSII) underwent a clinical study consisting mainly of two events: an interruption of pump insulin infusion and a standard meal with insulin bolus and basal insulin infusion. Both cases reproduce situations of real life. Model parameters were estimated by a simplex algorithm in order to fit study data. Then PD controllers were virtually tested and compared with the usual insulin therapy (basal infusion plus pre-prandial boles). Other realistic events were simulated: an unexpected increased amount of carbohydrates intake in the meal and slow changes in insulin sensitivity.

Results: The Root Mean Square (RMS) errors on blood glucose values between estimated and experimental data less than 2 mmol/l testify a good quality of estimation procedure. PD controllers performances were comparable to traditional therapy but showed better glycaemic profiles and an improved robustness i.e. the capability of coping with changes in meal composition and insulin sensitivity.

Conclusion: The positive results of estimation procedure show that personalization is the right way to get a reliable model. The analogy of responses between traditional therapy and PD controller suggests that a closed-loop control could be feasible not only in basal conditions, but even for driving a wearable artificial pancreas during post-prandial hyperglycemia and in many situations of real life.

A Prospective, Randomized, Multi-Centered Controlled Trial to Compare the Annual Outcomes of Patients with Diabetes Mellitus Monitored with Weekly Fructosamine Testing versus Usual Care: A Six Month Interim Analysis

Alan W. Carter, Pharm.D.* and Cameron C. Lindsey, Pharm.D.

*5600 Hedge Lane Terrace, Shawnee, KS, 66109
Tel: (913) 745-0013 • Fax: (913) 905-3027
Acarter29@cs.com

Introduction: The utilization of the fructosamine test for management of patients with diabetes mellitus remains unclear. The primary objectives of this study are to compare the quarterly A1C results of subjects monitoring weekly fructosamine to those receiving usual care, identify the number of patients achieving goal A1C, and to determine if the addition of a weekly fructosamine test changes a patient's quality of life.

Methods: This is a prospective, randomized, multi-center controlled trial. Patients were randomly assigned to collect weekly fructosamine in addition to daily glucose (Group 1) or usual care of daily glucose (Group 2) and had study visits every three months. Baseline and quarterly A1C tests were collected.

Results: Sixty subjects have been randomized into the study since May 2001 with enrollment ongoing. Baseline demographics, glucose, fructosamine and A1C were similar between the two groups. While a clinically significant change at the three-month interim analysis was observed there was no statistically significant difference in fructosamine ($p=0.265$) between groups. At six months, this improvement was statistically significant ($p=0.032$) for Group 1 (249.06 mmol/L +/- 66.06) versus Group 2 (314.79 mmol/L +/- 96.3). No statistical difference at three-months ($p=0.676$) and six-months ($p=0.183$) in A1C values for Group 1 (7.755% +/- 1.408 and 7.373% +/- 1.299) and Group 2 (7.971% +/- 1.797 and 8.236% +/- 2.046) were noted, however, at six months a trend toward significance was observed.

Conclusion: The interim data suggest that the fructosamine group had a net decrease in A1C over the six-month timeframe whereas the control group has had a net increase in A1C values. Ongoing follow-up will determine if this trend continues and becomes statistically and clinically significant.

Mhc Class II-peptide Chimeras for Identification and Down-Regulation of Diabetogenic CD4 T Cells

Sofia Casares[1] and Teodor-Doru Brumeanu

[1]Assistant Professor
Department of Microbiology, Mount Sinai School of Medicine
One Gustave L. Levy Place, Anbg Bldg. Box 1124, New York, NY 10029
Tel: 212-2419777 Fax: 212-8284151
sofia.casares@mssm.edu

Type 1 diabetes is an organ-specific autoimmune disease that is mediated by autoreactive T cells. We showed that administration of a soluble, dimeric MHC-II/peptide chimera (DEF) to prediabetic double transgenic mice prevented the onset of disease or reversed the disease in animals already diabetic. Mechanistically, the antidiabetogenic effects of DEF rely on the induction of anergy in splenic autoreactive CD4 T cells in the context of alteration of early TCR signaling, i.e., negative regulation of ZAP-70 kinase, and stimulation of IL-10 secreting T regulatory type 1 (Tr1) cells in pancreas. Similarly, human DEF chimeras made up of HLA-DR*0401 and peptides from GAD65 and proinsulin polarize specific T cells from HLA-DR-matched diabetic patients toward the Tr1 phenotype and IL-10 secretion. These chimeras are also suitable reagents for identification and immunocharacterization of autoreactive CD4 T cells in the blood of diabetic patients.

The MHC class II-peptide approach may be useful in the development of new tools for early diagnosis of the disease as well as antigen-specific therapies for Type 1 Diabetes.

Using the Diasnet Metabolic Model as an Integral Part of an Ambulatory Education Programme for Type 1 Diabetes, and for Ongoing Decision Support via the Internet

Cavan D A[1], Hejlesen O K[2], Plougmann S[2]

[1]Bournemouth Diabetes and Endocrine Centre
Royal Bournemouth Hospital
Bournemouth, BH7 7DW, UK
Tel: +44 1202 704610 • Fax: +44 1202 704759
david.cavan@rbch-tr.swest.nhs.uk

[2]MIBA
Aalborg University
Frdeik bajers Vej 7D
DK - 9220 Aalborg, Denmark
Tel: +45 9635 8808 • Fax: +45 9815 4008

We have developed an intensive education programme for patients with Type 1 diabetes. The aim is to teach carbohydrate counting and insulin dose adjustment over four, weekly, group sessions. Prior to each session, patients complete a four-day diary of food intake, insulin doses and blood glucose levels. These are entered into the Diasnet metabolic model, which displays patient data, simulates blood glucose profiles, and can demonstrate the effect of changes in meal size or insulin dose, and which we have previously shown can help improve diabetic control. At each session, patient data are displayed in Diasnet and projected for the whole group to view. Diasnet is used to help optimise each patient's insulin regime for the following week. Preliminary data suggest that the programme is effective in improving patients self-management skills (assessed using Ipswich questionnaire $p<0.001$) and overall diabetic control (HbA1c improved from 9.6 to 8.7% $p<0.001$), and this improvement is maintained for at least six months. As with any educational intervention, the goal is to maintain these improvements in the long term. In order to facilitate this, Diasnet is available via our website (www.b-dec.com) to enable patients to enter data from home once they have completed the programme. We have piloted its use by 6 patients, all of whom were able to enter their own data, although a number requested prompts to help take them through the process of data entry and interpretation. Once these have been incorporated, we will evaluate the effectiveness of access to Diasnet via the internet in maintaining good glycaemic control.

Simulation with 40 minute Delay in Glucose Measurements Demonstrates Feasibility of a Closed Loop Control using Subcutaneous Measurement and Subcutaneous Insulin Infusion During Fasting

L.J Chassin*, ME Wilinska, R.Hovorka

*Corresponding author
City University, MIM Centre, Northampton Square
London Ec1v Ohb, United Kingdom
l.chassin@soi.city.ac.uk

Background and Aims: Intensive insulin therapy using continuous subcutaneous insulin infusion is more efficacious than multiple daily injections. Closed loop control with online glucose measurement could automate glucoregulation by optimising insulin infusion in the presence of subject-dependent insulin response, infusion and measurement errors. A Model Predictive Control (MPC) showed efficacy with delay-free measurements simulations and clinical tests. Here we aim at assessing MPC performance with delayed measurements.

Materials and Methods: 18 synthesised virtual subjects were represented by a set of parameters, 5% variation with 3 and 24 hour periods representing a wide range of rates of temporal variations were added. Subjects were used in a test scenario simulating subcutaneous infusion of insulin Lispro and subcutaneous glucose measurements with 40min delay and 5% measurement error. After standardised meal (40g CHO) and insulin bolus at 9am, subjects were controlled manually until 1:00pm followed by MPC control until 8:30pm.

Results: Average glucose from beginning of MPC control, for last 5 and 3 hours of the experiment were 7.6±0.2, 7.4±0.2, and 7.3±0.2mmol/L (mean±SE), respectively. Maximum glucose from MPC start was 9.2±0.3, and 8.5±0.2 and 8.1±0.2mmol/L for the last 5 and 3 hours respectively. Minimum glucose from MPC start was 6.3±0.2, 6.5±0.2 and 6.5±0.2mmol/L (mean±SE) for last 5 hours and 3 hours experiment respectively. During last 3 hours, 4 subjects presented glucose variation over 2mmol/L, and 2 over 3mmol/L. Overall maximum and minimum glucose for last 3 hours were 11.1 and 3.7mmol/L, and 13.2 and 3.7mmol/L from MPC start respectively.

Conclusions: Simulations showed large fluctuations in some cases but indicate MPC ability to maintain glucose oscillations within clinically acceptable range demonstrating safety and efficacy under fasting condition with SC-SC route.

Use of the Sand Rat (Psammomys obesus) Multi-disciplinary Pathophysiology Studies: Collaborations and Partnerships

V. Michelle Chenault, Ph.D.[1], Carol Pugliese

[1]Office of Science and Technology, Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd. (HFZ-100), Rockville, MD 20850
Tel: (301) 827-4780 • Fax: (301) 827-4787
vmc@cdrh.fda.gov

The Animal Model

The animal, Psammomys obesus, belongs to the family Cricetidae, subfamily Gerbillinae (gerbils). It is called the 'fat sand rat' and inhabits the desert areas of the Middle East and Africa. Sand rats are not commercially available from rodent farms and is a unique rodent in that it develops nutritionally induced mild to moderate obesity, hyperglycemia and the complications of diabetes such as cataracts. pancreatic atrophy, impaired renal function, ketoacidosis and possibly sensorineural hearing loss by dietary modification. The animal also naturally develops aural cholesteatomas, osteoarthritis, spondylosis and intervertebral disc degeneration. P.obesus is unlike rodents in the genus Rattus in that it has a gallbladder. Investigators have proposed that the sand rat has a more efficient pathway of lipogenesis, useful during times when food is scarce. This animal model for diabetes is currently being used at a variety of research laboratories and universities for to facilitate the understanding of the pathophysiology of diabetes mellitus. This poster provides an overview of the studies in progress at the National Aeronautics and Space Administration,Cleveland, OH; L.V. Prasad Eye Institute in Hyerabad, India; Carolinas Medical Center; Marine Biological Laboratory in Woods Hole, MA and Uniformed Services University of the Health Sciences in Bethesda, MD. All the studies are in cooperation or collaboration with the Food and Drug Administration, Center for Devices and radiological Health.

Diabetes Disease Management Program for an Indigent Population Empowered by Telemedicine Technology

Julie Cheitlin Cherry, R.N., MSN
(corresponding author)

Medical Director, Health Hero Network, Inc.
2570 W. El Camino Real, Suite 111
Mountain View, California 94040
Tel: (650) 559-1094 • Fax: (650) 559-1050
jcherry@healthhero.com

Tracey P. Moffatt, RN, BSN, MHA
(presenter)

Vice President, Mercy Health Center
1515 Logan, Laredo, Texas 78040
Tel: (956) 796-3152
tmoffatt@laredo.mercy.net

Christine Rodriguez, RN, MSN

Telemedicine Coordinator, Mercy Health Center
1515 Logan, Laredo, Texas 78040
Tel: (956) 796-3152
tmoffatt@laredo.mercy.net

Kirsten Dryden

Marketing Director, Health Hero Network, Inc.
2570 W. El Camino Real, Suite 111
Mountain View, California 94040
Tel: (650) 559-1187 • Fax: (650) 559-1050
Kdryden@healthhero.com

Mercy Health Center implemented a telemedicine disease management program for patients with diabetes to determine the impact of a web-based, patient interface technology. The study assessed the effect of the intervention on the health of indigent border residents with diabetes. Using the Health Hero® iCare Desktop™ and the Health Buddy® appliance, patients were monitored daily at home and nurses were alerted if patients reported abnormalities. The goals of the program were to decrease hospital-based utilization; improve patient compliance, patient satisfaction and patients' perceived quality of life.

The study was conducted in calendar year 2000-2001 using comparative cohort data from calendar year 1999. After one year, reductions in overall utilization and charges, as well as improvements in quality of life were demonstrated. Results showed a reduction in overall charges of $747 per patient per year. Inpatient admissions were reduced 32% ($p < 0.07$), emergency room encounters were reduced 34% ($p < 0.06$), post discharge care visits were reduced 44% ($p < 0.28$), and outpatient visits were reduced 49% ($p < 0.001$).

Quality of life was assessed using the SF-12 survey conducted before and, respectively, quarterly for two quarters within the program. The mean improvement in the mental component after six months was 3.61 (from 45.00 to 48.61). The mean improvement in the physical component was 2.6 (from 41.83 to 44.42).

These reductions can likely be attributed to the patient's enhanced self-management behaviors and the nurse's ability to intervene in a timely manner when warranted. The remote monitoring technology facilitated prevention, education and early intervention. The daily communication bridged the gap between office visits for the patients and the early intervention ultimately reduced the cost of care.

A Telemedicine EMR for Diabetes Disease Management

Dr. Gildred Colón

American Telemedicine Center Corp.
The New San Juan Health Centre
Ave. De Diego #150, Suite 702, San Juan, Puerto Rico 00907
Tel: 787 721-5424 Fax: 787 721-5420
info@drcolon.com
http://www.drcolon.com

Purpose: To demonstrate the first EMR for diabetes disease management for a telemedicine setting.

Content: Eight modules in an EMR cover evidence-based diabetes disease management concentrating in the annual screening of the chronic complications of diabetes and the cardiovascular risk factors. Each module has a history (past and present) pertinent exam which when completed by a satellite center, all modules are submitted to HUB. Endocrinologists and ophthalmologists at HUB submit the diagnosis and recommendations for treatment. Once completed, the patient is interviewed by videoconference and satellite center prints out the summary of the evaluation.

Highlights: In the module of retinopathy screening, the image of the retina extracted from a digital retinal camera, will be saved annual. Also, any foot or skin lesions obtained from a digital camera will be saved in the module of neuropathy and diabetic foot or the module of interim consultations. The EKG tracing and analysis of automatic cardiac neuropathy will be saved annually in the module of cardiovascular screening. Results of tests, exams and outcomes can be compared from year to year. In a telemedicine setting, the EMR would be used by the PCP at the satellite center consulting endocrinologists and ophthalmologists at the HUB center. The EMR could also be used with the HUB serving as an Application Service Provider and not as consultants.

Limitations: The highest costs involves obtaining network partners and establishing the telecommunications lines.

Utilization of the Intelligent Dosing System (IDS) Software Suite for Management of Insulin Therapy in Urban Diabetes Patients

Curtiss B. Cook[1], Linda J. Mann[2], Esther C. King[2], Katina New[2], Pamela Vaughn[2], Tina Allen[2], Jane M. Caudle[2], Virginia G. Dunbar[2], Christopher D. George[2], John P. Mcmichael[3]

[1]Diabetes Clinic, Emory University School of Medicine
69 Jesse Hill Jr, Dr., Atlanta, GA 30303
Tel: 404 616-3716 • Fax: 404 616-3717
cbcook@emory.edu

[2]Grady Health System
96 Armstrong St., SE Atlanta, Ga, 30303

[3]RxFiles Corporation
342 Tamiami Trail South, Nokomis, FL 34275
941 483-3784

Many practitioners are uncomfortable with insulin pharmacotherapy. The IDSTM is a software suite that uses patient specific, treatment dose response data in an equation that calculates the new dose of agent to achieve the next desired therapeutic goal. We conducted a study to evaluate applicability of the IDS for adjusting insulin doses in an urban diabetes clinic. To construct the insulin IDS model, retrospective dose-response data were retrieved from our computerized patient registry. Observed values of hemoglobin A1c (HbA1c), fasting blood glucose (FBG), and random blood glucose (RBG) were separately input as target markers into the IDS, which then calculated the next insulin dose needed to achieve these levels, these calculated doses were compared to those actually prescribed. When HbA1c was used as the marker (n=185), the average agreement between the IDS calculated and prescribed insulin dose was 102 ± 33% (r=0.93). For FBG (n=186), average agreement was 105 ± 30% (r=0.95), and 102 ± 31% (r=0.96) for RBG (n=40). We next conducted a prospective study to evaluate use in patient care. The insulin IDS was placed on a hand held platform, then provided to practitioners for adjusting total daily insulin at the point of care. The FBG achieved was compared to the IDS predicted value. Among patients where prescribed and calculated insulin doses differed by only ±5% (n=61), the average agreement between predicted and achieved FBG was 103 ± 15%, with good correlation (r=0.91). There was no difference between average predicted (154 mg/dl) and achieved (151 mg/dl) FBG (p=0.24). These analyses suggest that use of the IDS may be a valid approach to standardize insulin dosing and assist in attainment of glycemic goals. Continued prospective evaluation is underway.

This work was supported in part from a grant from the RxFiles Corporation

The SMSI Continuous Glucose Monitoring System

Anthony W. Czarnik, Ph.D.

Sensors for Medicine and Science, Inc.
12321 Middlebrook Road STE 210
Germantown, MD 20874-1518
Tel: 301-515-7260 • Fax: 301-515-0988
awczarnik@s4ms.com
http://www.s4ms.com

The SMSI Glucose Monitoring System (SGMS) consists of two components: a subcutaneous sensor implant about twice the size of a grain of rice, and an external device that assumes the form factor of a watch, a pager, or a patch. The sensor implant is a microfluorimeter that is inductively powered and remotely interrogated; the surface of the implant is coated with a glucose-selective fluorescent chemosensor. The system works as follows: (1) every two minutes, the external device powers the implanted fluorimeter "through-space"; (2) the fluorimeter delivers excitation energy to the fluorescent chemosensor; (3) the fluorimeter measures the fluorescence of the chemosensor; (4) the fluorimeter sends that information to the external device; and (5) the external device calculates the glucose level, and displays and stores the glucose reading. The sensor is expected to remain implanted for at least six months, with a target lifetime of one year. In this way, a diabetic patient will require only a short invasive procedure in a physician's office to receive six months to one year of continuous glucose measurements. Infrequent fingersticks may be used to confirm the accuracy of the system over the course of the implant lifetime.

TANDEM: Information Technology for Education and Management of Young Patients with Type 1 Diabetes Mellitus (T1DM)

G. d'Annunzio[1]*, M. A. Zanetti[2], C. Pennati[1], S. Montani[3], S. Cetta[3], R. Bellazzi[3]

[1]Dept of Pediatrics, IRCCS Policlinico San Matteo, P.le Golgi 2, I-27100 Pavia
Tel: +39/0382/502930-50850 • Fax: +39/03827527976
gdannunzio@smatteo.pv.it
(*presenting author)

[2]Dept. of Psychology, University of Pavia, P.zza Botta 6, I-27100 Pavia
Tel: +39/0382/506275
zanetti@unipv.it

[3]Dept. of Computer and Sistemic Sciences, University of Pavia, Via Ferrata 1, I-27100 Pavia
Tel: +39/0382/505511 • Fax: +39/0382/505373
ric@aim.unipv.it

Educational process, the cornerstone for T1DM patients and their families to reach better knowledge in disease management and self-esteem, is based on individual needs and capability to learn. TANDEM is a team-based information technology (IT) assisted educational project for youngsters with T1DM. The team included 2 pediatricians (PH1 and PH2), a psychologist and 3 computer scientists, 7 patients (3 males , 4 females, aged 14.4+/-3.7 years, disease duration 5.3+/-2.7 years, HbA1c mean levels 7.9+/- 0.9%, n.v. 3.5-5.5%), their relatives (Treated Group, TG); 7 patients, matched for age, disease duration, degree of metabolic control, their relatives were Control Group, CG. The intervention consisted of 6 meetings with the TG, where all the main topics about T1DM were explained; between each meeting TG communicated with physicians and themselves reporting their personal experiences in a Web-based discussion group. An IT-based chat group, available over the Web, was accessible by a PC or a WebTV. The tool, written in PL-SQL, relied on Oracle Web Server. The psychologist delivered to TG, CG, their parents and physicians a questionnaire (semi-structured interviews), about disease perception and management, social aspects, global self-value (self-efficacy questionnaire, SEQ). TG and CG had a higher score vs PH1 ($p<0.05$) and CG vs PH2 ($p<0.05$), reflecting patients' positive perception of T1DM and its management. Physicians underestimated patients' social integration. TG shoved a higher score vs parents ($p<0.01$), reflecting parents' emotional involvement. TG and CG showed similar HbA1c values before and after the intervention, but TANDEM represented a unusual tool to improve quality of care, and allowed to explicit by information technology some problems related to educational and social aspects of T1DM, sometimes neglected in routine clinical practice.

Statistically-based Csii Parameters: Correction Factor, Cf (1700 Rule), Carbohydrate-to-insulin Ratio, Cir (2.8 Rule), and Basal-to-total Ratio

Paul C Davidson*, Harry R Hebblewhite, Bruce W Bode, R Dennis Steed, N Spencer Welch, M. Carol Greenlee, Pat L Richardson, and Joe Johnson

*Paul_C_Davidson@msn.com

A database of 497 insulin pump patients was analyzed to derive parameters for optimal diabetes management. These formulae are given the name "The Pump Groove Formulae".

DATA: Total daily dose of insulin (TDD) from pump's memory, average, standard deviation and frequency of BG from patient's BG meters, and CF, CIR, BW#, and HbA1c from the medical records.

STATISTICAL PLAN: Analyze a sample of well-controlled patients in search of parameters that will be applicable for all patients. The sampling included a well-controlled group--HbA1c<7% and >6 months' pump experience--and a complement of the remaining database. The size of the well-controlled sample was 141. The studies involved determining the slope through the origin for each individual.. The median of all the slopes was used as the slope of the fitted line. This method was less sensitive to outliers than using least squares or mean slope. T-tests were run between the well-controlled sample and its complement

RESULT:

	Standard Error	T-test
CF=1724/TDD	12	P=.04
CIR=2.8*BW#/TDD	3.7	P<.01
Basal=0.48*TDD	5.4	P=0.6

RECOMMENDED USE: Adjust parameters of subjects incrementally toward Pump-Groove goals.

THREE MONTHS' FOLLOW-UP STUDY:
21 patients were chosen with HbA1c>8 despite competent self-monitoring. They were readjusted biweekly using the Pump-Groove formulae. The initial and final values of the group mean HbA1c and BGmean were compared using T-tests:

	HbA1c	BGmean
Initial	8.16	178
Final	7.38	150
T-tests	P<.0.0001	P<0.0001

Admittedly, it is difficult to distinguish the effect of the Pump-Groove formulae from the study effect.

Diabetes-related Luminescent Assays for Multi-analyte Measurement

Rupert H. Davies and Joseph D. Andrade*

Department of Bioengineering
University of Utah
2480 Merrill Engineering Building
50 South Central Campus Drive
Salt Lake City, Utah 84112 USA
rupert.davies@m.cc.utah.edu and joeandrade@uofu.net
* Corresponding author/presenter

Luminescent-based enzymatic analysis can potentially measure a wide range of metabolites with the same device. Most metabolites of interest can be coupled to a luminescent detection system. Compared to existing analytical systems, luminescent-based detection systems need approximately 100 times less sample fluid volume to measure equivalent concentrations. However, luminescent-based analysis remains underutilized as a metabolic diagnostic method for multi-analyte devices. We are currently developing a variety of luminescent-based analytical assays that will be combined on a hand-held device. Our goal is to develop quantitative analytical systems for the measurement of up to 50 analytes in 50 microliters or smaller volumes of physiologic fluids, such as blood and urine. Ultimately, if the potential of luminescent-based assays were realized, nearly all biochemicals could be quantitatively and specifically measured in small volume samples via relatively inexpensive, reliable instruments in the point-of-care environments.

Glucose and creatinine are important in the diagnosis, management and treatment of diabetic patients. Creatinine has been included because diabetes is the number one cause of kidney disease and a third of all diabetics may ultimately develop a form of kidney disease. Glucose and creatinine are both measured by coupling enzymatic reactions (glucokinase; creatininase and creatine kinase; respectively) to the bioluminescent firefly luciferase reaction. In both cases the light measured is proportional to the concentration of the analyte in the sample. The glucose and creatinine assays need only small sample volumes and have been lyophilized to increase storage stability and ease of application.

We would like to acknowledge the support of NIH RFA# PAR-01-057, Project# RR17329, Technology Development for Biomedical Applications Grant and our industrial partners.

Analysis of Continuous Glucose Monitoring Data From Healthy Children: A Tale of Two Algorithms

Maria C. DeLucia[1], Elizabeth A. Boland[2], and William V. Tamborlane[3]

[1]Presenter
c/o 24 Brentwood Dr., Wallingford, CT 06492
Tel: (203) 785-4648 or (203) 288-0540
maria.delucia@yale.edu

[2]Correspondent
Doctors Building, 2 Church Street South, Suite 312
New Haven, CT 06520
Tel: (203) 764-6650 • Fax: (203) 764-8464
elizabeth.boland@yale.edu

[3]Yale University School of Medicine
3103 LMP, PO Box 208064, New Haven, CT 06520-8064
Tel: (203) 785-4646
william.tamborlane@yale.edu

Our experience with the MiniMed Continuous Glucose Monitoring System (CGMS) in healthy, non-diabetic children uncovered a surprising number of low and high sensor values, raising concerns that the 1.6 analytical algorithm might be over-reading glycemic excursions. A new software program (version 1.7) for analysis of sensor data was recently introduced. Our study objective was to compare analysis of the same sensor profiles using the two programs. Twenty-five healthy, non-diabetic children were studied (age 14 + 4 years); data are presented as mean + SD; night values = 12am-6am.

	Version 1.6	Version 1.7	p value
# Sensor Readings	694 + 224	750 + 160	.022
Sensor Glucose (SG) mg/dL	103 + 24	100 + 14	.370
%SG < 70 mg/dL	13.8 + 10.4	8.2 + 7.9	.000
%SG 70-150 mg/dL	78.5 + 13.0	87.2 + 10.3	.000
%SG > 150 mg/dL	7.7 + 12.4	4.7 + 8.8	.020
%Night SG < 70 mg/dL	25.8 + 25.0	17.9 + 18.3	.064
%Night SG > 150 mg/dL	9.4 + 18.3	4.0 + 12.5	.126

Although the mean absolute difference was only 2.6 + 5.6%, the 1.6 software identified more frequent lows and highs than the 1.7 software. A similar analysis of profiles from 41 children with type 1 diabetes revealed no significant differences between the two software programs in detection of hypo- and hyperglycemia (data not shown). Conclusion: In non-diabetic children, the 1.7 software may be particularly useful in preventing over-reading of low and high sensor readings, whereas both programs give similar results in children with diabetes.

Minimally Invasive, and Convenient Infusion Set for Insulin Delivery

Joel Douglas

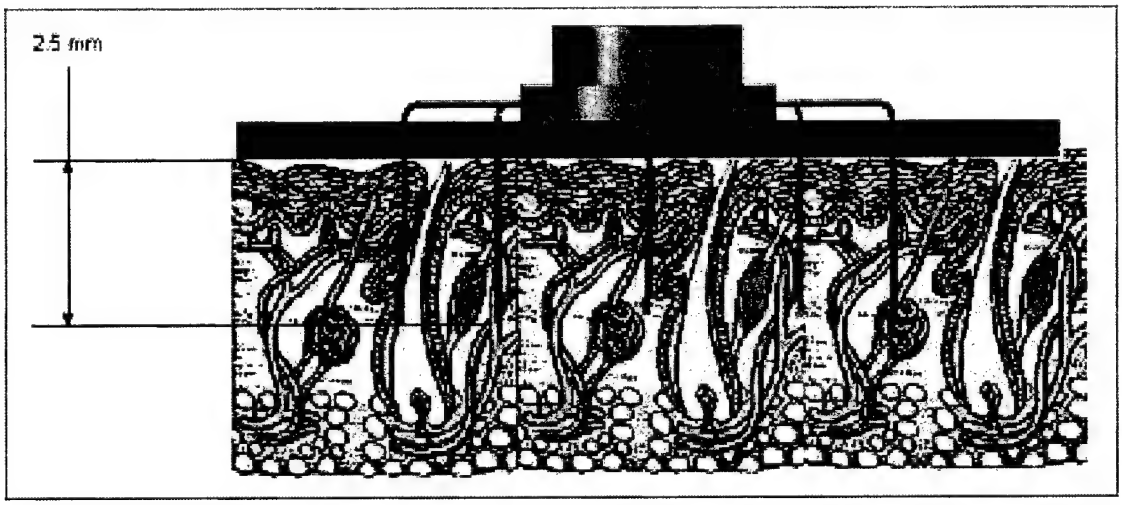
Simple Choice, a SpectRx company
25285 La Loma Drive, Los Altos Hills, CA 94022
Tel: 650-814-4083 • Fax: 650-949-0342
jdouglas@spectRx.com

Background: Substantial progress has recently been made in the area of blood glucose monitoring to make it more convenient, less painful and easier to perform. However, insulin dependent people with diabetes using insulin pumps must still insert a 6 - 9 mm cannula to provide a means of infusing insulin. Improvements in insulin infusion have not kept pace with rapid improvements in glucose monitoring.

Methods: Discussions with groups of patients and in one-on-one sessions, determined that patient's feel that the current state of insulin infusion sets does not fill the needs of insulin pump patients. Patient concerns were reflected by these various sub-groupings: a) I am pain adverse, b) Why must the indwelling infusion cannula be so long?

Results: SpectRx has completed development and received FDA clearance for a new minimally invasive insulin delivery patch that allows an insulin pump patient to infuse their insulin with indwelling cannulae that are only 2.5 mm in length. This provides a more comfortable experience and less pain associated with infusing insulin.

Conclusions: The SpectRx insulin infusion set patch product is the first of a new generation of minimally invasive insulin delivery devices that SpectRx is developing to diminish pain and improve the quality of life for people with diabetes.



Inference of Blood Glucose Concentration for Control

Francis J. Doyle III and Camelia L. Owens

University of Delaware, Newark, DE 19716
Department of Chemical Engineering

211 Colburn Laboratory
University of Delaware, Newark, DE 19716
Tel: 302-831-0760 • Fax: 302-831-0457
fdoyle@udel.edu

A number of mathematical models of the diabetic patient have been developed to describe the dynamic insulin-glucose relationship characteristic of the disease. Among these are the Bergman model and the Automated Insulin Dosage Advisor (AIDA) that are minimal models of the diabetic patient incorporating meal and insulin dynamics in their framework. It is apparent that the key to proper glucose control is the delivery of the optimal amount of insulin at the correct time based on an accurate measurement of the blood glucose concentration. However, directly measuring blood glucose concentrations from the bloodstream poses the risk for severe infection at the measurement site. An alternative is to use a more feasible measurement site such as the subcutaneous tissue to prevent such infections. From the subcutaneous blood glucose measurements, the actual blood glucose concentration can be inferred based on a model of the transport limitations between the bloodstream and the subcutaneous tissue.

The transport model employed to infer blood glucose concentrations accounts for the diffusive transport of glucose from the bloodstream to the subcutaneous tissue and the reactive-like cellular uptake of glucose in the subcutaneous tissue. With the subcutaneous glucose measurements and a transport model, the blood glucose concentrations can be estimated with an observer. Proper estimation of the blood glucose level will depend upon the tuning of the observer. With the use of Model Predictive Control (MPC) or other closed-loop techniques, the blood glucose levels of the diabetic patient can be controlled within euglycemic limits.

Accessibility of Blood Glucose Monitoring Systems for Blind and Visually Impaired People

Kh. Eghtesadi, Ph.D.[1], M. Uslan, D. Burton, A. Spiker[2], K. Schnell[3]

[1]Tech for All, Inc., Wilton, Connecticut, www.tech-for-all.com
[2]School of Medicine, Marshall University, Huntington, West Virginia
[3]College of Science, Marshall University, Huntington, West Virginia

AFB TECH, American Foundation for the Blind
949, 3rd Ave, Huntington, WV 25701
KEghtesadi@aol.com

Sixteen blood glucose monitoring systems were evaluated for accessible use by people who are blind or visually impaired. Features and functionalities such as: blood sampling mechanisms, operating procedures, user interface design, electrical requirements, mechanical specifications, and computer interface capabilities were examined and tabulated as was usability and accessibility. Blind and visually impaired users of these systems were selected, interviewed, and videotaped using the devices. Key accessibility barriers were identified and demonstrated. A subset of these systems with a high degree of accessibility was selected and thoroughly examined and tested. It was determined that a majority of commercially available blood glucose monitoring systems have accessibility limitations for people who are blind or visually impaired. Recommendations were made for design and development that would remove these barriers.

Monitoring Blood Glucose Control in Type 2 Diabetic Patients in a Developing Country

*Chidum E. Ezenwaka, Risha Kalloo

Unit of Pathology & Microbiology, Faculty of Medical Sciences,
The University of the West Indies, St Augustine, Trinidad, W.I.
Fax: 1-868-663-3797
ezenwaka@tstt.net.tt
[Presenting & corresponding author]

Background: The task of blood glucose control in type 2 diabetic patients visiting primary healthcare clinics in developing countries is frost with problems of limited healthcare facilities and concomitant poverty among the patients.

Objective: To determine any difference in the glycemic control of the same group of type 2 diabetic patients previously studied at two primary health care clinics in Trinidad.

Method: 78 previously studied type 2 diabetic patients were re-assessed for glycemic control after two years of an initial evaluation. After an overnight fast, waist and hip circumferences (cm), height (m) and weight (kg) were measured. A 7 ml venous blood sample was taken from each patient for plasma glucose and glycated hemoglobin (HbA1c) measurements.

Results: The overall mean HbA1c level increased significantly from mean value of 9.7% to 10.6% ($p < 0.05$) and only 3.8% of the patients re-assessed had HbA1c levels < 7.0%. Although insignificant, female patients had a relatively higher percentage of patients with generalized obesity (BMI > 30kg/m2), abdominal obesity and poor glycemic control than the male patients on re-evaluation ($p > 0.05$).

Conclusion: The results suggest that the task of blood glucose control in diabetic patients in the developing countries might remain elusive if urgent and sustained intervention strategy is not instituted at primary care clinics.

Reduction of Stress through the use of the Quantum Biofeedback System

Cynthia R. Fena[2], Dr. Pravin Patel[1]

[1]2160 University Dr. #A7
Vista, CA 92083
Tel: 760 - 724-2002
aleia@worldnet.att.net

[2]20681 Calloway Dr. 314-119, Bakersfield, CA 93312
Tel: 661 - 589-3917 • Fax: 888 - 717-0351
saikepree @bak.rr.com

This paper examines the application of a computerized system as a means to reduce stress and therefore to reduce the symptoms of and need to medicate for diabetes.

Due to the presence of experimental controls necessary for the protection of internal validity, the standard factorial design experiment is not well suited to an examination of the complexities of studying stress, so a case study, while weaker for reliability, was selected.

The choice for treatment of stress was the Quantum Biofeedback system (QXCI device), a highly complex computer program which measures stress as energetic components in the body. With a feedback loop, it records the patient's frequency pulse and sends back an alternate pulse to which the body responds. In turn, the body alters its own frequency pulse, thus creating a change in the body's response to the stress.

The QXCI device was used to treat a 49-year-old female subject having Type I diabetes for 30 years with no documented complications. She exhibited a HBA1C of <7.0 for the last 3 years, being treated with intensive insulin therapy of Lantus as a basal, and 4-6 injections of Humalog as boluses. She was undergoing stress in the form of applying to graduate school, finalizing a divorce and moving during the time of this study.

Results included a 48% reduction in insulin intake, an HbA1C of <7.0, reduction of pulse BP from 112/78 to 110/68, and alleviated other stress symptoms, which produce elevated blood glucose levels, and can proceed the development of diabetes related complications.

Automatic Extraction of Risk Indexes as a Basis for a New Model of Management of Diabetes Mellitus by Telemedicine

P. Ferrari, R. Bellazzi*, I.Zunino, P.DeCata, G.Clerici, S.Giordanetti, C.Gazzaruso, C.Larizza* M.Stefanelli*, P.Fratino

Correspondence Authors:
Pietro Ferrari, Clinical Fellow, pferrari@fsm.it
Riccardo Bellazzi, PhD, Riccardo.Bellazzi@unipv.it

Internal Medicine, IRCCS Fondazione S. Maugeri, Pavia, Italy
Via Ferrata 8, Pavia, 27100, Italy
Phone: 39-0382-592715 • Fax: 39-0382/592079

* Dipartimento di Informatica e Sistemistica, University of Pavia, Pavia, Italy

Background: To implement telemedicine systems in clinical practice it is necessary to couple technological solutions with new process-of-care measures, able to quickly and automatically summarize the overall patients' status. AIM: Within the M2DM telemedicine project, funded by the European Commission, the aim is to implement and test a new integrated model of patient management, based on individual metabolic targets fixed by physician and on use of a set of indexes automatically generated by the system. The goal is to prove that a dynamic picture of the risk status of the patient, together with process-of-care measures, should be an effective and quick instrument for improving clinical outcome in a telemedicine context.

Methods: The following indexes have been considered for 20 insulin treated diabetic subjects M2DM enrolled: mean BG, mean postprandial BG, standard deviation BG, M-value, MAGE, mean FBG. Each measure (in absolute value) become part of a set (vector) of indexes I1, ..., Ii,..., In. All values may be reported into a [0 1] scale by a logistic transformation, so that it is possible to obtain the singular risk index SRI= 1/(1+exp-K(I1- I01))-0.5, where I01 is a target value dependent to the patient and K is a suitable constant; negative values of I1-I01 are taken as 0. In this way it is possible to obtain a Global Risk Indicator (GRI) by averaging the single SRI. GRI gives a global instantaneous indicator of developing microvascular complications. The indexes are currently evaluated within the project.

Conclusion: In the management of diabetes mellitus by telemedicine the use of an automatically generated, synthetic and always repeatable index of metabolic status is feasible, it simplifies the care-intervention and it is likely to improve the overall usefulness of telemedical interventions.

Application of Bacterial Fructosyl-amine Oxidase for Measurement of Glycated Hemoglobin, HbA1c

Stefano Ferri, Akane Sakaguchi, Wakako Tsugawa, and Koji Sode

Department of Biotechnology, Tokyo University of Agriculture & Technology
2-24-16 Naka-cho, Koganei-shi, Tokyo, 184-8588 Japan
Tel/Fax: +81-42-388-7030

stefano@cc.tuat.ac.jp
akanes86@aol.com
tsugawa@cc.tuat.ac.jp
sode@cc.tuat.ac.jp

Corresponding author/presenter: Stefano Ferri (stefano@cc.tuat.ac.jp)

Maintaining normal blood glucose levels is important in preventing the chronic complications of diabetes. The glycated hemoglobin HbA1c, an indicator of glycemic control, is routinely measured by HPLC, affinity chromatography, or immunoassay methods. To satisfy the great demand for a simple and economical alternative for POC application, our group has been investigating the development of enzyme sensors to measure HbA1c. We previously reported on the construction of different types of amperometric sensors for fructosyl-valine, a model compound for HbA1c, employing a fructosyl-amine oxidase (FAOD) isolated from the marine yeast Pichia sp. N1-1 strain (1, 2, 3). These remain the only reports of enzyme sensors for HbA1c and we continue to actively search for novel catalysts capable of detecting fructosyl amine compounds.

We now report on a recently isolated bacterium capable of growing aerobically in minimal medium supplemented with fructosyl-valine as the sole nitrogen source. An FAOD was purified from the bacterium and found to have high activity with fructosyl-valine but no activity with Nefructosyl-lysine, a model compound for glycated albumin. We cloned the FAOD gene and successfully expressed it in E. coli. Utilizing the recombinant enzyme, an electrode was constructed based on hydrogen peroxide oxidation at 600 mV vs. Ag/AgCl. This FAOD-based electrode exhibits high sensitivity and a good linear correlation between 1 mM to 1 mM fructosyl-valine, giving it great potential for application in the measurement of HbA1c.

(1) Tsugawa W, Ishimura F, Ogawa K, Sode K (2000) Electrochemistry 68:869
(2) Tsugawa W, Ogawa K, Ishimura F, Sode K (2001) Electrochemistry 69:973
(3) Ogawa K, Stöllner D, Scheller F, Warsinke A, Ishimura F, Tsugawa W, Ferri S, Sode K (in press) Anal Bioanal Chem.

Quantitation of Physiologic Variability During Experiments with an External Closed-Loop Glycemic Control System

Paul Galley*[1], Robin Wagner[1], Harvey Buck[1], Stefan Weinert[1], Kym Marco[1], Steven Bousamra[2], and Jane Bridges[3]

*Presenter
[1]Roche Diagnostics Corporation
9115 Hague Road, Indianapolis, Indiana 46250
Tel: (317) 521-3473 Fax: (317) 521-3060
Paul.Galley@Roche.com
Robin.Wagner@Roche.com
Harvey.Buck@Roche.com
Stefan.Weinert@Roche.com
Kym.Marco@Roche.com

[2]System Design Group, Inc.
8739A Castle Park Drive, Indianapolis, Indiana 46256
Tel: (317) 598-8556 Fax: (317) 598-8532
sbousamra@systemdesigngroup.com

[3]Good Samaritan Hospital
Welch Diabetes Center
615 Dubois St., Vincennes, Indiana, 47591
Tel: (812) 885-8040 Fax: (812) 885-8043
HgbAlc@aol.com

Introduction: Normal, day-to-day physiologic variability in individuals may pose difficulties for glucose control algorithms. Therefore, experiments were conducted to assess physiologic variability under regulated clinical conditions and to estimate the possible impact of variability on algorithm-directed glycemic control.

Methods: Eight study subjects with Type 1 diabetes participated in three 33-hour long experiments conducted with an external closed-loop glycemic control system. Algorithm parameters were individualized for each study subject based on prior experimental results and were not changed during these experiments. Study subjects selected meals and snacks from a fixed menu and consumed the selected meals at consistent times during all experiments. An individual's experiments took place at 3-6 week intervals. Retrospective analysis was performed to determine the optimal amount of insulin required for each meal and the coefficient of variation was determined. Data from 7 of 8 study subjects are presented pending completion of all experiments.

Results: Data are the coefficient of variation of the optimal insulin requirement for each meal.

Study Subject	#1	#2	#3	#4	#6	#7	#8
Breakfast	6%	5%	10%	10%	7%	9%	9%
Lunch	15%	4%	5%	3%	0%	6%	1%
Supper	5%	6%	3%	2%	12%	5%	8%

Conclusions: Under regulated clinical conditions, optimal insulin requirements for meals vary from meal to meal and among individuals with greater variation at breakfast. We expect this variation represents the combined influence of intervals between experiments, insulin absorption and pharmacodynamics, differences in gastric emptying, nutrient absorption, and other undefined factors. Greater variations in optimal insulin requirement are expected with free choice meals, carbohydrate estimation, and throughout the menstrual cycle which may pose challenges to a closed loop glycemic control system.

Middleware Technologies for Telemedicine-based Diabetes Shared Care

Angel García-Olaya, Enrique J. Gómez, M. Elena Hernando, F. Javier Perdices, Francisco del Pozo

Grupo de Bioingeniería y Telemedicina
Universidad Politécnica de Madrid
Ciudad Universitaria S/N
28040 Madrid (Spain)
agarcia@gbt.tfo.upm.es
egomez@gbt.tfo.upm.es
elena@gbt.tfo.upm.es
fjperdic@gbt.tfo.upm.es
fpozo@gbt.tfo.upm.es
Phone: +34-91- 3367308 / +34-91- 549-57-00 ext 332 • Fax: +34-91-336-68-28
Presenter: Enrique J. Gómez

Shared care of diabetics is a continuous process requiring a tight interaction between the patient and the diabetes care team. The Electronic Health Record is the basis to support shared care. However, the success of these care programmes leans not only on the viability to provide powerful clinical and monitoring data collection/access platforms, but collaboration information systems to support care team members are also needed. The application of Computer Supported Collaborative Work (CSCW) theories and tools to build telemedicine systems can be a valuable aid to bear diabetes shared care.

This work aims to introduce a Middleware Architecture that, relying on the Electronic Health Record (EHR), will ease the development of applications that allow performing the Integrated Care of a patient.

The system architecture is comprised of two middleware layers that act as an interface with the EHR to the concrete shared care telemedicine applications. The Multi-Access bottom layer provides the tools to collect and deliver patient related data to users. This layer is in charge of the interoperability with the EHR. A CSCW Layer, supported by the previous one, provides asynchronous collaborative services to facilitate the team work. Both layers allow the construction of telemedicine-based workspaces for diabetes care allowing care plan definition and monitoring, EHR access and data register, Short-term therapy definition, Shared information dissemination, Events and activities notification, Visits and meetings scheduling, etc. The middleware architecture is currently integrated in the M2DM project, funded by the EU, and it will be tested in Hospital Sant Pau at Barcelona (Spain).

Glucose Monitoring System in Patients with Type 1 Diabetes Mellitus after Islet Cell Transplantation

Milene C Geiger*, Jacqueline V. Ferreira Tatiana Froud, Aileen Caulfield, David Baidal, Lisa Rothenberg, Norma S.Kenyon, Camillo Ricordi, Rodolfo Alejandro

Diabetes Research Institute,
University of Miami, 11450 NW 10th Ave Room 2061 Miami/ FL 33136
Fax: 305 243 1058
mgeiger@med.miami.edu Tel: 305 2431059 (*Presenting author)
jferreir2@med.miami.edu Tel: 305 243 2228
tfroud@med.miami.edu Tel: 305 2433390
Acaulfield@med.miami.edu Tel: 305 2431059
dbaidal@med.miami.edu Tel: 305 2433469
Lrothenb@med.miami.edu Tel: 305 2432879
mgeiger@med.miami.edu Tel: 305 2435364
Cricordi@med.miami.edu Tel: 305 2436913
Ralejand@med.miami.edu Tel: 305 2435324

Purpose: CGMS was recently introduced as a technique for monitoring blood glucose in diabetic patients but its use has not been reported in patients receiving islet cell transplants.

Methods: We monitored the metabolic control in 6 patients that received islet cell transplantation and 4 control subjects using the CGMS. We evaluated the frequency and the circadian rhythm of hypoglycemia and blood glucose excursions after meals.

Patients received human cultured islets and were on steroid-free immunosuppressive regiment. The transplant subjects were between 122-352 days post-transplant, age averaged 38.2 ±4.5 years in study group versus 36 ±7.8 years in control group.

Results: The glycemic excursions after meals averaged 57.60 ±35.75 mg/dl for breakfast, 68.65 ±35.70 mg/dl for lunch, and 35.25 ±24.14 mg/dl for dinner in the study group and were higher than the control group which averaged 24.82 ±12.84 mg/dl, 20.81 ±6.17 mg/dl and 28.65 ±13.52 mg/dl for breakfast, lunch and dinner respectively. Four out of six study subjects had at least one episode of low blood glucose lasting at least one hour, including one male. All four control subjects had low blood glucose episodes; most of them were nocturnal and lasted more than one hour.

Conclusions: The CGMS is a more useful system to evaluate the peak glycemic excursion and the duration of hyperglycemia in post transplant subjects when compared to finger-sticks. Patients and controls were comparable as to timing of post meal glycemic peak between 1-3 hours post-meal, however in post transplant patients the peak was higher and prolonged, something that was not detected using finger-stick alone.

Patients also had nocturnal episodes of low blood glucose, but not as many as the control subjects.

Non-Invasive Monitoring of Encapsulated Beta Cell Function Using Mn^{2+}-Enhanced Magnetic Resonance Imaging

Barjor Gimi*[1], Lara Leoni*[1], Sertac Eroglu[1], Tejal Desai[1,2], Richard L. Magin[1], Brian Roman[1,3]

[1]Department of Bioengineering, University of Illinois at Chicago
Science and Engineering Offices (M/C 063),
851 South Morgan Street, Chicago, Illinois 60607-7052, USA
Tel: +1 312 996 2335 Fax: +1 312 996 5921
Barjor Gimi- bgimi1@uic.edu
Lara Leoni- lara@uic.edu
Sertac Eroglu- serogl1@uic.edu
Richard L. Magin- rmagin@uic.edu

[2]Department of Biomedical Engineering, Boston University
44 Cummington Street, Boston, Massachusetts 02215, USA
Tel: +1 617 358 3054 Fax: +1 617 353 6766
tdesai@bu.edu

[3]Department of Physiology and Biophysics, University of Illinois at Chicago
College of Medicine (M/C 901),
835 South Wolcott Avenue, Chicago, Illinois 60612-7342, USA
Tel: + 1 312 355 1624 Fax: +1 312 996 5921
Broman@uic.edu

* Corresponding authors

The immunoisolation of pancreatic beta cells has emerged as a promising therapy of treating Type I diabetes. Currently, several micro and macro-encapsulation devices are under investigation. The efficacy of these devices is assessed via measurement of serum glucose levels, which provides no direct information on the graft functional volume and on the formation of necrotic islet-cells.

In light of clinical needs, it is critical to develop non-invasive techniques that can help study the in-vivo implant efficacy, and periodically assess functional status and viability of the encapsulated cells.

Magnetic resonance (MR) imaging is a non-invasive modality that provides information of anatomy as well as function. Glucose stimulation of beta cells induces calcium influx, through L-type calcium channels. Manganese acts as a calcium analog and can enter these cells in the same manner. Manganese is also a very good MR relaxation/ contrast agent. In this study we show that subtoxic doses of manganese provides differential signal enhancement in cells activated by glucose stimulation. This selective contrast is important in obtaining a functional map of the graft, which can be correlated with metabolic information. Furthermore, the use of unique microfabricated transceiver coils enables us to obtain near single-cell resolution of the implant image. Subsequent localized spectroscopy may provide simultaneous information on numerous metabolites within both activated and non-activated regions.

With the use of this imaging technique, we were able to successfully characterize encapsulated beta cell activation in response to glucose stimulation. We believe that this information will help in optimizing encapsulation device design and performance.

Oral Insulin Absorption with Emisphere® Drug Delivery Agents & Mechanistic Studies Using Intestinal Epithelial Cells

Isabel Gomez-Orellana*, Robert Angelo, Dmitry Malkov, Heather Tang, Huai-zhen Wang, Elizabeth Flanders, and Steve Dinh

Emisphere Technologies, Inc.
765 Old Saw Mill River Road
Tarrytown, NY 10591
Tel: 914-785-4775
igomez@emisphere.com
(*) Correspondence author.

Emisphere Technologies has developed a series of low molecular weight compounds (Delivery Agents) that enable safe and efficient absorption of orally administered insulin. These oral insulin formulations present many important advantages over current technology, including convenience, cost-effectiveness, stability, and ability to deliver insulin directly into the portal circulation. The mechanism of oral insulin absorption with these Delivery Agents has been investigated using Caco-2 cells, a well-characterized cell model for oral drug absorption. Fluorescence microscopy studies showed that insulin is absorbed transcellulary when applied to the apical surface of monolayers in conjunction with Delivery Agents. No changes in TEER, mannitol permeability, or perijunctional ring appearance were observed during insulin transport, indicating that tight junctions are not affected by the presence of the Delivery Agents. Measurements of LDH release revealed that the integrity of the plasma membrane was not compromised during insulin absorption. Together these results indicate that insulin absorption is selective, transcellular, and does not involve plasma membrane or tight junction disruption.

Comparison of an Automated Nerve Conduction Testing System to Conventional Studies in Patients With Diabetes Mellitus

Shai N. Gozani, M.D., Ph.D.,[1,2], Mark S. Emley, M.S.,[1] Aaron I. Vinik, M.D., Ph.D,[3]

[1]NeuroMetrix, Inc., Waltham, Massachusetts.
[2]Harvard-MIT Division of Health Sciences and Technology, Cambridge, Massachusetts.
[3]The Leonard Strelitz Diabetes Research Institutes, Departments of Internal Medicine and Pathology/ Anatomy/Neurobiology, Eastern Virginia Medical School, Norfolk, Virginia.

Mark Emley
NeuroMetrix, Inc.
62 Fourth Ave, Waltham, MA 02451
781-890-9989 & 781-314-2714 direct • Fax: 781-890-1556
memley@neurometrix.com

Aaron Vinik, MD, PhD
Eastern Virginia Medical School
Diabetes Institute
855 West Brambleton Avenue, Norfolk, VA 23501
(757) 446-5912

Corresponding/Presenting Author
Shai N. Gozani, MD, PhD
NeuroMetrix, Inc.
62 Fourth Ave
Waltham, MA 02451
Tel: 781-890-9989 & 781-314-2789 direct • Fax: 781-890-1556
gozani@neurometrix.com

Introduction. Diabetic polyneuropathy (DPN) is among the most common and disabling chronic complications of diabetes mellitus. Nerve conduction studies (NCS) provide early and objective evidence of DPN, however they are not used regularly for logistical and economic reasons. The recent development of an automated nerve conduction testing system (NC-statÒ, NeuroMetrix, Inc.) creates the opportunity to incorporate NCS methods into the management of diabetic patients. This device utilizes prefabricated active biosensors, a small automated instrument and a telemedicine system to deliver accurate and reliable NCS at the point-of-patient care. Prior studies of this system demonstrated high correlations to conventional techniques. In the present study, performance in a diabetic population was assessed.

Methods. Seventeen patients with Type II diabetes mellitus and clinical evidence of peripheral neuropathy were evaluated. Each subject received a conventional and NC-stat upper extremity nerve conduction study consisting of distal motor latencies (DML) and F-wave latencies in the median and ulnar nerves. The conventional study was performed by a technician under supervision of a neurologist.

Results. The mean age of the subjects was 50.2 years, and all had a history consistent with DPN. The correlation between DMLs measured by the NC-stat and the conventional NCS was 0.96 for the median nerve and 0.70 for the

ulnar nerve. The corresponding correlations for the F-wave latencies were 0.89 and 0.79. All correlations were significant ($p<0.005$).

Discussion. This study demonstrates that high correlations between NC-stat and conventional NCS reported in prior studies are maintained in a diabetic population. Additional comparative studies in the lower extremities and for sensory nerve conduction measurements would be helpful in further clarifying the utility of this tool in managing diabetic patients.

Neurophysiological Measurements to Noninvasively Monitor Blood Glucose: Demonstration of Proof of Concept

Shai N. Gozani, MD, Ph.D.[1], Alan C. Moses, M.D.[2]

[1]Corresponding/Presenting Author
NeuroMetrix, Inc.
62 Fourth Ave, Waltham, MA 02451
Tel: 781-890-9989 & 781-314-2789 direct • Fax: 781-890-1556
gozani@neurometrix.com

[2]Joslin Diabetes Center
One Joslin Place, Boston, MA 02215
Tel: (617) 732-2502
Alan.Moses@joslin.harvard.edu

Introduction. The Diabetes Control and Complications Trial (DCCT) demonstrated that intensification of diabetes therapy with the goal of normalizing blood glucose concentration reduces long-term diabetes associated morbidity. Frequent self-monitoring of blood glucose is a key component of achieving near normoglycemia. Since most current monitoring methods utilize discrete capillary sampling, the need for adjunctive semi-continuous tracking exists. The present study investigated the use of noninvasive peripheral nerve responses as such an indicator. We hypothesized that like glucose-related electrical oscillations in heart muscle and pancreatic beta cells, peripheral nerves are subtly but detectably influenced by blood glucose.

Methods. Eight three-hour experiments were conducted in four subjects with type 2 diabetes. Each subject was studied with a hyperglycemic and hypoglycemic protocol. Blood glucose concentration was perturbed in a controlled manner and monitored at 5 to 15 minute intervals (YSI). Neurophysiological measurements, consisting of sub-maximal median nerve sensory potentials, were made at 15-30 minute intervals. In five of eight studies, sufficient numbers of high signal-to-noise nerve measurements were acquired and processed further. Calibration to blood glucose concentration was achieved using principal component regression (PCR).

Results. Low frequency (0.01 - 0.06 Hz) glucose dependent oscillations in nerve response amplitude were observed. The correlation with blood glucose concentration ranged from 0.90 to 0.93 (three at $p<0.05$, remaining two $p=0.08$ & $p=0.15$). A 0-21 minute time lag between neurophysiological responses and blood glucose was observed, particularly in the hypoglycemic protocol.

Discussion. The present study provides a preliminary indication that peripheral nerve response oscillations may encode blood glucose levels with a moderate delay. Such signals may be acquired noninvasively with low cost instrumentation and sensors. If further studies are supportive, this method may provide a means for semi-continuous monitoring of blood glucose concentration over short time intervals.

'Sweet Talk' Text Messaging System for Diabetes Support

Dr. Stephen Greene[1], Victoria Franklin[2], and Annalu Waller[2]

[1]Reader in Child & Adolescent Health, Tayside Institute Child Health
University of Dundee, Ninewells Hospital & Medical School
Dundee, Scotland DD1 9SY
Tel: (+44) 01382 660111 • Fax: (+44) 01382 633849
Pager: 07669 151833 Mobile: 07703 576526
(Work Univ) s.a.greene@dundee.ac.uk
(Work NHS) sagreene@tuht.scot.nhs.uk
(Home) sgreenestandrews@aol.com

[2]Child Health and Applied Computing, University of Dundee, Dundee, Scotland, UK

Optimal diabetes management involves considerable behavioural modification and non-adherence contributes significantly to poor glycaemia. Extensive research on psychological interventions aiming to improve glycaemia suggests that current strategies are costly, time-consuming and in our experience do not appeal to young people with Type 1 diabetes. Text messaging has rapidly become a socially popular from of communication. It is personal, highly transportable and used, particularly, in the adolescent population. Text Messaging coupled with specific behavioural health strategies has yet to be utilised effectively.

We have developed a novel support network ("Sweet Talk"-ST), based on a unique text-messaging system designed to deliver general diabetes information, but in particular individualised motivation strategies based on social learning theory.

In a randomised control trial we are investigating the impact of "ST" on the efficacy of intensive insulin therapy (multiple injections and/or pumps). No support is being compared with ST alone and ST plus intensive therapy. Treatment goals related to diabetes management are set in the clinic between health carers and patients, and reinforced between visits by specific daily text messages. Young people will also be able to write their own motivational messages. Measurements of outcomes include: HbA1c, clinical progress, psychological measures and acceptability and use.

Intensifying insulin therapy and increasing contact with the diabetes team can improve control, but are difficult to provide within existing resources. Our support system we believe offers a means of contact and support between clinic visits aimed to increase adherence with intensive insulin regimens and to improve clinical outcome.

Supporting Diabetes by the Telephone: An RCT on the Effect of Negotiated Telephone Support on Young People with Diabetes

Dr. Stephen Greene[1], Lesley Howells[2], Chas Skinner[2], Andrew Morris[2], Ray Newton[2]

[1]Reader in Child & Adolescent Health, Tayside Institute Child Health
University of Dundee, Ninewells Hospital & Medical School
Dundee, Scotland DD1 9SY
Tel: (+44) 01382 660111 • Fax: (+44) 01382 633849
Pager: 07669 151833 Mobile: 07703 576526
(Work Univ) s.a.greene@dundee.ac.uk
(Work NHS) sagreene@tuht.scot.nhs.uk
(Home) sgreenestandrews@aol.com

[2]Child Health and Medicine, University of Dundee, Dundee, Scotland, UK

Aim: To evaluate the impact of 'Negotiated Telephone Support' (NTS) on clinical and psychological outcomes (self-efficacy) in Type 1 diabetes in young people.

Method: The NTS intervention was developed using the principles of problem solving and social learning theory. One-year RCT (n=79, m 39; mean age 16.5 yr., duration 6.7 yr., HbA1c 8.6%) randomised into: Group 1 (Control group), routine management, n=28; Group 2 routine management with NTS, n=25; Group 3 annual clinic with NTS, n=26. Outcome measures: HbA1c, self-efficacy, barriers to adherence, problem solving, and diabetes knowledge.

Results: Participants in groups 2&3 received an average of 16-telephone calls/yr. (range 5-19), median duration 9 min. (2-30), with a median interval of 3 wk. (1-24) between calls.

Significant correlations were found between age and average length of call ($r=0.44$, $p<0.01$) and frequency of contact ($r=0.36$, $p<0.05$). Social and school topics were discussed frequently. After 1 year, while the participants in the two intervention groups showed significant improvements in self-efficacy ($p=0.035$), there was no differences in glycaemic control.

Barriers to insulin adherence predicted HbA1c ($p<0.001$) after controlling for baseline.

Conclusion: NTS is an effective medium to deliver a simple theory-based psychological intervention to enhance self-efficacy for diabetes self-management. Reduced clinic attendance, combined with NTS, did not result in a deterioration of HbA1c. The Telephone is capable of delivering a psychological based support programme. However, intensive personal support should be combined with intensive therapy to improve glycaemic control.

Non-Enzymatic Glucose Biosensor for Continuous Measurement

In Suk Han*[1], Young Jun Lee[1], Man-Hee Han[1], Seok Lew[1], Jinwon Kim[1], Jules J. Magda[2]

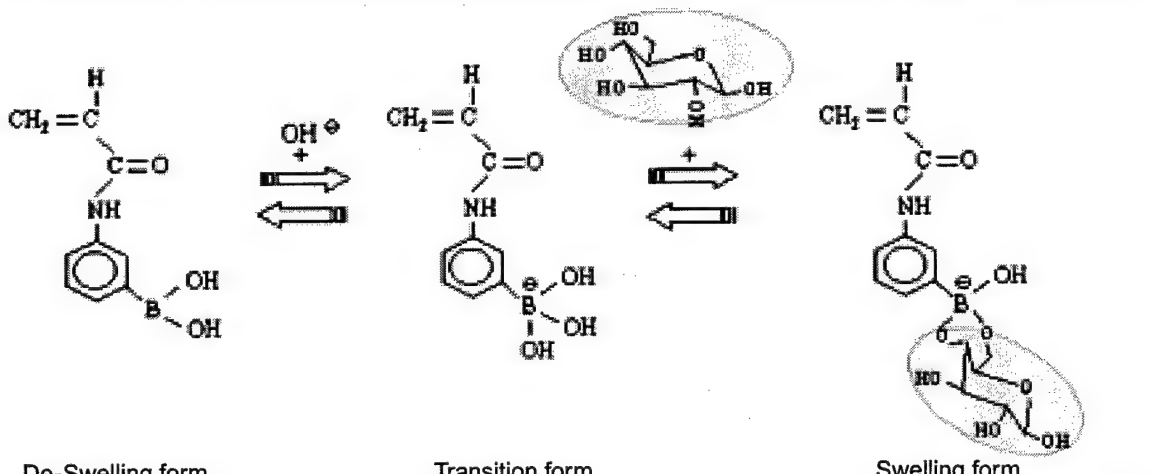
[1]M-Biotech, Inc., Metrobusiness Park
2411 South 1070 West, #C, Salt Lake City, Utah 84119, USA

[2]Department of Chemical and Fuels Engineering, University of Utah
Salt Lake City, Utah 84112, USA

*M-Biotech, Inc.
2411 South 1070 West, Suite C, Salt Lake City, UT 84119
Tel: 801-975-0747 • Fax: 801-975-0746
ishan@m-biotech.com

Since most glucose biosensors currently being developed employ the enzyme, glucose oxidase, they are subject to significant limitations such as enzyme degradation and oxygen deficit for carrying out the oxidation reaction. At M-Biotech, we have developed non-enzymatic glucose biosensor based on glucose-sensitive hydrogel (GSH) and a pressure sensor. The GSH is mainly composed of phenylboronicacid (PBA) as glucose binding molecules, dimethylacrylamide as a hydrophilic backbone material, and N,N-methylenebisacrylamide as a crosslinking agent. The GSH swells according to the level of glucose molecules. The main driving force for swelling in the GSH is the increase in the charge density incurred by glucose binding to the PBA moieties (Figure 1). The GSH is confined to measure pressure changes as an osmotic pressure function between the diaphragm of a pressure transducer and a semi-permeable membrane through which glucose in a fluid can pass. We continuously measured the swelling pressure of the GHS in a confined chamber with a pressure transducer. The swelling pressure of the GHS is proportional to the concentration of free glucose (0~600 mg/dL) both in PBS buffer solution and in goat serum. This novel glucose sensor will avoid the problems of enzyme-based biosensors such as oxygen deficit and enzyme deactivation. Other potential advantages of M-Biotech's biosensor include continuous monitoring capability, a high specificity to glucose, and a longer life time.

Figure 1. The Equilibria of acrylamide phenylboronicacid (AAmPBA) in an aqueous solution in the presence of glucose



Optical Bridge Noninvasive Bgm

Harjunmaa, Hannu, Ph.D.*, Kun, Stevan, Ph.D.*^, Lock, J. Paul, M.D.*,
and Peura, Robert A., Ph.D.*^

*VivaScan Corporation, 560 Prospect St., West Boylston, MA 01583, 508-852-1600 (phone),
harjunmaa@earthlink.net, skun@alum.wpi.edu, jplock@massmed.org, rpeura@aol.com

^Biomedical Engineering Department, Worcester Polytechnic Institute, 100 Institute Road, Worcester,
MA 01609 Tel: 508-831-5596 • Fax: 978-464-5683
rpeura@aol.com

Corresponding author: Robert A. Peura, Ph.D., President VivaScan Corporation, 560 Prospect Street,
West Boylston, MA 01538, Tel: 508-852-1600 • Fax: 978-464-5683
rpeura@aol.com

Our goal is to develop a noninvasive glucometer for diabetic individuals. The technology platform is based upon the Optical BridgeTM (OB), which uniquely measures a chemical analytes of interest while suppressing the undesirable background signal.

Unlike conventional spectrophotometric methods that record the absorbance at a number of single wavelengths and then apply mathematical techniques to interpret the spectrum, the OB records directly the changes in transmittance differences across wavelength pairs as the blood content of the tissue sample is changed using external forcing. Typically, at least one of the wavelength pairs has a glucose-sensitive and a glucose-insensitive wavelength. The time-varying amount of blood in the sample is measured independently. The differential absorption data is combined with the blood data, thus effectively making the resulting glucose estimate largely independent of the speed and magnitude of the blood content change.

The OB is an optical Wheatstone bridge equivalent. It differentially measures minute alterations in the optical absorption of a sample at two wavelengths. This methodology may be used for measurements of various body fluid analytes. For glucose, we beam two near-infrared lights (1620nm-high sensitivity and 1380nm-low sensitivity to glucose) through the earlobe. The change in glucose concentration is effected by the displacement and re-entry of blood in the sampling site, by controlled squeezing and unsqueezing. Measurements (579 data points) were recorded over the span of 82 days on 14 subjects. 96% of all data points were within the Clarke A & B regions, which is considered to be of acceptable clinical accuracy for diabetes management. The average measurement error was 23%, or 33 mg/dl.

Laboratory Testing for Glycated Hemoglobin and Microalbumin in the General Community: Are We Following the Clinical Recommendations?

Todd S. Harwell, MPH, Randie R. Little, PhD, Janet M. McDowall, RN, BSN, Steven D. Helgerson, MD, MPH, Dorothy Gohdes, MD

[1](Corresponding author)
Montana Department of Public Health and Human Services, Cogswell Building, C-317
PO Box 202951, Helena, Montana 59620-2951
Phone: (406) 444-1437 • Fax: (406) 444-7465
tharwell@state.mt.us

[2]University of Missouri-Columbia, School of Medicine
One Hospital Drive, Room M767, Columbia, Missouri 65212
Phone: (573) 882-1257 • Fax: (573) 884-8823
littler@health.missouri.edu

[3]Montana Department of Public Health and Human Services, Cogswell Building, C-317
PO Box 202951, Helena, Montana 59620-2951
Phone: (406) 444-6677 • Fax: (406) 444-7465
jmcdowall@state.mt.us
epiaction@aol.com
dgohdes@aol.com

Objectives: To describe laboratory practices for glycated hemoglobin (GHb) and microalbumin (MA) testing in Montana.

Methods: In 2002, all laboratories in Montana as well as identified reference laboratories were surveyed by mail to ascertain if they provided testing for MA and glycated hemoglobin, the exact tests performed, units and cutoffs used to report MA results, awareness of the National Glycated Hemoglobin Standardization Program (NGSP), and the number of tests performed in the past month.

Results: One hundred and three of the 126 laboratories responded to the survey (82%). Forty-four percent of these laboratories reported currently testing for GHb. Of laboratories that test for GHb, most reported results as HbA1c (98%). Less than half of responding laboratories that provided glycated hemoglobin testing were aware of the NGSP (42%), although 71% of laboratories used methods certified by the NGSP. Because large laboratories performed the majority of tests, 99% of GHb test results were performed with NGSP certified methods. Twenty-five (24%) laboratories provided quantitative testing for MA on site. Sixty-one percent of these laboratories provided A/C ratio testing and reported their results in the units and cutoffs recommended by the American Diabetes Association and the American Association of Clinical Chemistry. Fewer laboratories provided 24-h (33%) or timed (25%) testing and reported results using the recommended units and cutoffs.

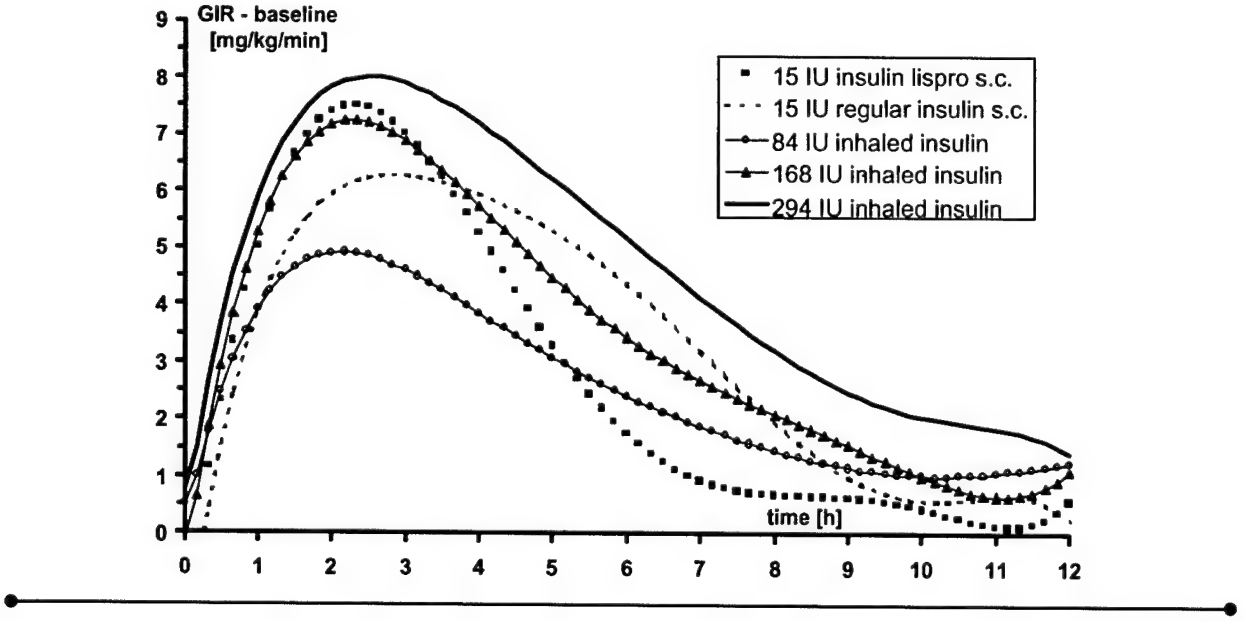
Conclusions: Glycated hemoglobin testing is routinely offered by Montana laboratories and reported correctly as % HbA1c; most tests are performed with NGSP certified methods and were therefore traceable to results from clinical outcome studies. MA testing is offered less routinely by Montana laboratories - and the results are often reported in units and cutoffs that differ from the current clinical recommendations.

Time-Action Profile of a New Rapid Acting Inhaled Insulin with High Biopotency

Lutz Heinemann[3], Chester Osborn[1], Rick Batycky[2], Alka Verma[1], Corinna Tusek[3], Susanne Bott[3], Tim Heise[3]

[1]Alkermes Europe Ltd., UK
[2]AIR Inc., MA, USA
[3]PROFIL Institute for Metabolic Research
Hellersbergstr. 9, Neuss, Germany 41460
Tel: 49 2131 4018 402 • Fax: 49 2131 4018 502
lutz.heinemann@profil-research.de

This study investigated the time-action profile and dose-response relationship of a rapid acting, dry powder, inhaled insulin (AI) developed by Alkermes using its propriety AIR technology. The pharmacodynamic properties of AI at 84, 168 and 294 IU was investigated by means of euglycemic glucose clamp (clamp level 5.0 mmol/L, continuous i.v. insulin infusion of 0.15 mU/kg/min, clamp duration 12 hours post-dosing) in comparison with 15 IU s.c insulin lispro (IL) and with 15 IU s.c regular insulin (RI) in 12 healthy male volunteers (non smokers, age 28.9 ± 5.9 years, BMI 23.5 ± 2.3 kg/m2). AI showed a faster onset of action compared with s.c insulin (early $T_{Max\,50\%}$: 29 (84 IU); 35 (168 IU); 33 (294 IU); 41 (IL), 64 (RI) [$p<0.1$ for 84 IU vs. IL, $p<0.05$ for AI (all doses) vs. RI]). AI demonstrated a linear dose response indicated by a steady increase in AUC-GIR0-720 min , and GIRmax ($p< 0.01$ for linearity). AI 294 IU generated a total metabolic effect 70% greater than 15 IU IL ($p<0.01$). AUC-GIR0-180 for 84 IU was comparable to 15 IU giving a biopotency over a typical meal related period of 23.3%. Total biopotency of 84 IU AI was 18% compared with RI and 18% compared with IL. There were no effects on pulmonary function. Inhalation of AI was safe, well tolerated and demonstrated a rapid onset of action, linear dose response relationship and high bioefficacy. The small, convenient and inexpensive inhaler together with a room temperature stable powder makes for an attractive replacement for currently available injections.



Detection of Unrecognised Hypoglycaemia in Type 1 Diabetes by the DiasNet Model of Carbohydrate Metabolism

Hejlesen OK*[1], Plougmann S[2], Cavan DA[3]

(*Corresponding author/presenter)
[1]Department of Health Science and Technology, Aalborg University
Fredrik Bajersvej 7D, DK-9220 Aalborg, Denmark
Fax: +4598154008 • Phone: +4596358808
Email: okh@mi.auc.dk

[2]Department of Health Science and Technology, Aalborg University
Fredrik Bajersvej 7D, DK-9220 Aalborg, Denmark
Fax: +4598154008 • Phone: +4596358782
Email: spp@hst.auc.dk

[3]Bournemouth Diabetes and Endocrine Centre, Royal Bournemouth Hospital
Bournemouth, BH7 7DW, UK
Phone: +44 1202704610 • Fax: +44 1202704759
Email: david.cavan@rbch-tr.swest.nhs.uk

We have assessed the feasibility of using the DiasNet model of carbohydrate metabolism to identify unrecognised hypoglycaemia in patients with Type 1 diabetes by comparing the system with data from the MiniMed subcutaneous glucose sensor. The DiasNet model can help identify unrecognised hypoglycaemia. This can be done directly by using the predicted blood glucose profile and indirectly by detection of a long-term hypoglycaemic counter-regulation (hypo-counter). The latter is described in our previous studies, and in a typical hypo-counter measured blood glucose levels are elevated by 4 to 10 mmol/l for 16 to 18 hours beginning 6 to 8 hours after the hypoglycaemic episode, giving a total duration of 24 hours or more. 13 patients collected data on insulin injections, carbohydrate intake and blood glucose levels for 3 consecutive days while wearing a MiniMed glucose sensor. Analysing the standard data using DiasNet alone (blind to the sensor data) suggested 11 patients with hypoglycaemic episodes, even though four had no measured values below 3.5 mmol/l. DiasNet suggested that only two had no evidence of unrecognised hypoglycaemia. These findings were then compared with the sensor data. In the 11 patients with suspected hypoglycaemia, the sensor indicated 18 hypoglycaemic episodes (of which 9 were nocturnal), and all 11 patients had one or more hypoglycaemic episodes. The sensor also confirmed that the remaining two patients had no unrecognised hypoglycaemia. In conclusion, these data suggest that the DiasNet model may have a role in identifying patients with potential unrecognised hypoglycaemia, which may be verified by, for example, the MiniMed glucose sensor. The data furthermore support the existence of long-term hypoglycaemic counter-regulation as a common occurrence in patients with Type 1 diabetes.

MyCareTeam: An Internet Tool for Better Glucose Control

Ming-Jye T. Hu, MS, Betty A. Levine, MS, Karen E. Smith, MD, Adil Alaoui, MS, Stephen Clement, MD, Seong K. Mun, PhD

Georgetown University
ISIS Center
2115 Wisconsin Ave, NW #603
Washington, DC 20057
202-687-2643 (phone)
202-784-3479 (fax)
hut@georgetown.edu

MyCareTeam was developed to help people with diabetes better manage their disease and improve their access to their care providers over the Internet in between regularly scheduled clinic visits. Patients transmit blood glucose readings automatically to a secure database where they and their healthcare team access the results over a secure Internet connection. Other clinical information such as blood pressure readings, exercise and medication logs, and lab values are communicated as well. The site uses automated analysis of the blood glucose data along with alert messaging to enhance the patient's and care provider's interaction with the site.

MyCareTeam's graphical user interface mimics a clinic visit for the patient. Patients enter a virtual clinic, sign in with the receptionist and proceed to share their latest blood glucose readings with their care provider. A synopsis of their latest glucose readings, along with recent lab results and other clinical data is provided when the patient first authenticates into the system. Their blood glucose data is presented in multiple graphical formats to enhance the patient's ability to understand and learn from their own clinical data.

A feasibility study of MyCareTeam was undertaken at Georgetown University with remarkable results. The aim of the study was to reduce HbA1c by 1 point over a 6-month trial period. Sixteen patients were enrolled and were asked to send their blood glucose data weekly to and check their results on the MyCareTeam site. A statistically significant reduction in HbA1c over the 6-months was seen and will be presented. Two larger randomized control trials are currently underway to verify the results found under the feasibility study.

WinGlucofacts Professional v3.0: An Intelligent Diabetes Data Management System

D. Huang, B. Thompson

Bayer Corporation
1884 Miles Avenue, Building 18
Elkhart, IN 46514
Tel: 574 264 8918 • Fax: 574 262 6309
dijia.huang.b@bayer.com

WinGlucofacts Professional v3.0 with Data Wizard is a diabetes data management software program for the health care professionals (HCPs). It consists of two major systems:
• An intelligent diabetes data analysis and report generating system, based on the patented Intelligent Diabetes Data Interpreter technology.
• An electronic medical recording (EMR) system.

The data analysis and report generating system downloads the glucose readings from a patient' meter. It performs a long list of statistic analyses and pattern searching on the data set to detect significant trends and correlations. The system then generates a summary report based on these findings. The report is user configurable, from the simplest one-page summary to the full size version of nine sections. Each section presents the findings in a specific area, such as glucose trend, in the form of statements, graphs and tables. It is simple and intuitive to use: Just download a meter and press the keys. The data is automatically analyzed and a report comes out of the printer. The physicians and nurses can use the printed report as a basis for consultation and a record for the patient chart. It helps the HCPs to treat their patients more efficiently.

The EMR system stores patient information, medication records, lab results, complications status, diabetes education records, doctor's recommendation, etc. Its search and query functions allow a user to search patient files for various information and statistics. The search and query functions are particularly useful for aggregate outcome statistics, such as the data for the ADA recognition program.

Helping Patients to Succeed: Applying Handheld Technology to a Clinical Trial in Type I Diabetes

Michael R. Hufford, Ph.D., Orville Kolterman, M.D.

invivodata, inc.
2100 Wharton St., Ste. 505, Pittsburgh, PA 15203
Tel: (412) 390-3008 • Fax: (412) 390-2020
mhufford@invivodata.com

The reliable and valid capture of self-report data are increasingly important endpoints for the pharmaceutical industry in general, and diabetes trials in particular. These data have traditionally been collected using paper-based methods. This presentation reviews the application of handheld computers to clinical research by focusing on the science of Ecological Momentary Assessment (EMA; Stone & Shiffman, 1994; Hufford & Shiffman, 2002). EMA focuses on capturing real-time data from patients in the real world. Technology is used to support the scientific endpoints in EMA research. Data from a recent study published in the British Medical Journal (Stone et al., 2002) will be presented. These data confirm that handheld technology can help patients succeed in providing real-time data, whereas paper-based methods are vulnerable to both back-filling (recording entries just before the visit) as well as forward-filling (recording entries prior to the corresponding time and date). The potential for EMA to be used in diabetes research is illustrated by description of an on-going Phase II trial using Palm™-based devices to help patients adhere to the protocol. Patients are entering real-time data regarding their meals, pre- and post-meal blood glucose levels, insulin doses and study medication administration. Specifically, livability and compliance features used to drive patient adherence to the protocol will be presented. The importance of using web technology to track patients' adherence will be discussed and illustrated with relevant examples.

POC Glucose Control

Brad Hunsley and Wayne L. Ryan, Ph.D.*

*1606 S. 187th Circle, Omaha, NE 68130
Phone: (402) 691-7408 Fax: (402) 537-5352
jbuland@streck.com

The preparation of a glucose control for any of the wet chemistry methods is a precise analytical procedure in which the suspending medium plays little or no role in the final value. The preparation of glucose controls for the POC devices used for diabetes control are very different. Many of the characteristics of whole blood must be present to obtain accurate values with these instruments.

The earliest methods of providing glucose controls relied on the addition of metabolic inhibitors to fresh blood. The useful life of such controls is only a few days. Early attempts to make commercial glucose controls used serum and aldehyde-stabilized red blood cells. These controls usually gave stable values which were reproducible with any one strip, but between strips and different instruments the values differed greatly. Further, the values did not agree with the central laboratories analyses.

Our goals were to provide a glucose control that was stable, reproducible, and provided values within a few percent of the true value. To achieve these goals, it is necessary to provide a close simulation of the RBC and serum.

For example, the RBC can pass through a two micron filter in spite of its much larger size. An appropriate surrogate must produce the same effect as the elongated RBC. The control RBC movement through the filter must mimic whole blood because the diffusion of the glucose through the membrane is a rate-limiting step for the enzymatic reaction.

An example : glucose/H2O on YSI = 60 mg/dl. On a strip, glucose measures 175 mg/dl. Similar discrepancies are seen with serum. A new glucose Sugar-Chex II control gives good agreement with YSI and other instruments.

State Space Modelling of IVGTT and Insulin Clamps

Dr. Judith L. Jacobsen, PhD.

BioStatistics
Novo Nordisk A/S
Novo Alle 1, Building 9dS.12
DK - 2880 Bagsvaerd, Denmark
(+45) 4442 1637
jlja@novonordisk.com

The state space formulation offers a very attractive, intuitive method to model normo- and pathophysiological diseases such as diabetes. The models are defined as coupled, differential equations, using a priori knowledge of the physiological (here the metabolic) system and with the measured data as input. This form of modelling is called Grey box modelling and it is implemented in a program called CTSM (Continuous Timeseries Modelling). The parameters are estimated using the Maximum Likelihood method, in which the likelihood function is updated using the Kalman Filter. This method assures that the model makes sense, physiologically and fits the measured data very well, thereby describing, for example, the uptake, delivery/turnover and effect of insulin. The model may thereafter be used for simulation.

The method is implemented in two studies. An Insulin Clamp Model, where the glucose infusion rate (GIR) is an (almost) continuous input, used to determine the characteristics of two insulin analogues. The other implementation is a model for an IVGTT (intravenous Gloucose Tolerance Test), where Bergmans Minimal Model is formulated as a state space model.

This type of modelling may easily be adapted for continuous glucose monitoring with automatic insulin delivery and feedback control.

Conclusion:
- State space models formulated by differential equations are a promising way of modelling the dynamics of the insulin/glucose system.
- The advantage of using grey-box models is that the prior physiologic knowledge is combined with the information from the obtained data.
- More reliable information about the insulin/glucose system is obtained since all the available data is used in the estimation procedure.

Continuous Monitoring of the Subcutaneous Glucose Level in Freely Moving Normal and Diabetic Rats and in Humans with Type 1 Diabetes

Reza Jamali, M.D.[1], Johnny Ludvigsson, M.D., Ph.D.[2], Simin Mohseni, Ph.D.[3]

[1](Correspondent)
Division of Cell Biology, Department of Biomedicine and Surgery, Faculty of Health Sciences Linköping University
SE-581 85 Linköping, Sweden
Tel: +46-13-222796 • Fax: +46-13-223192
rezja@ibk.liu.se
[3]Tel: +46 13 22 41 44 • Fax: +46 13 22 31 92
simin.mohseni@hul.liu.se

[2]Division of Paediatrics, Department of Health and Environment, Faculty of Health Sciences Linköping University
SE-581 85 Linköping, Sweden.
Tel: +46-13-221333 • Fax: +46-13-148265
Johnny.ludvigsson@lio.se

Background: Laboratory animals, mainly rodents, are extensively used in diabetic research. However, it is not known whether the glucose dynamics in these animals is similar to the dynamics in human beings. The aim of the present study is to see whether the Medtronic-MiniMed continuous glucose monitoring system (CGMS) can be used to record the subcutaneous glucose level in freely moving normal and insulin-treated diabetic rats.

Methods: The monitoring system was applied during 3 days to normal (n=6) and diabetic hyperglycaemic (n=6) and hypoglycaemic (n=6) rats treated with subcutaneous insulin implants. Corresponding data from Type I diabetic patients (n=12) with poor glycaemic control were selected retrospectively in order to note the similarities and differences.

Results: We found that the monitoring system was convenient to apply and worked well in rats. In normal rats the subcutaneous glucose level had subtle variations with a median of 111 mg/dl (mean±SD=115±25 mg/dl). In hyperglycaemic rats the subcutaneous glucose values fluctuated markedly around a median of 226 mg/dl (mean±SD=231±98 mg/dl). The fluctuations formed a short-wave pattern with a low amplitude, superimposed on a long-wave pattern with a high amplitude. The subcutaneous glucose profile seen in Type 1 diabetic patients (median=180 mg/dl, mean±SD=191±97 mg/dl) was similar to that observed in hyperglycaemic rats.
In hypoglycaemic rats, the subcutaneous glucose level fluctuated moderately around a median of 55 mg/dl (mean±SD=66±35 mg/dl. In these rats the fluctuations formed a short-wave pattern with low amplitude, without any obvious long-wave pattern. The subcutaneous glucose values conformed to corresponding blood glucose measurements.

Conclusion: The Medtronic-MiniMed continuous glucose monitoring system can be used to record the subcutaneous glucose level over time in freely moving rats.

The National Insulin Pump Register in the Czech Republic

Z. Jankovec, D. Cechurova, S. Lacigova, M. Zourek and Z. Rusavy

Medical Department I., University Hospital, Pilsen, Czech Republic
312 00 Plzen
Czech Republic
jankovec@fnplzen.cz

Background and Aims: The register of patients treated by continuous subcutaneous insulin infusion was established in the Czech Republic in 1998. Our target was acquire the data of diabetic patients which are treated with continuous subcutaneous insulin infusion (CSII) to verify efectivity and safety of this way of treatment.

Materials and Methods: In this time there are the data of 1022 patients what were acquired by question-forms from 37 diabetology centers in the Czech Republic.

Results: The average age of diabetic patients is 40,5±13,94 years, duration of diabetes at start CSII 13,9±9,27 years. and duration of CSII treatment 3,6±2,80 years. Men constitute 48,3%, women 51,7% of patients, type 2 diabetics 8% of all patients. Reasons for treatment CSII: 77% (of all patient) chronical poor control of diabetes, 39% wish of patient, 39% diabetic neuropathy, 31% other late complication of diabetes, 17% dawn phenomenon and 12% insulin resistance (every patients may have more reasons). No other reasons get over 6%. Our results document the significant improvement of diabetes control. Mean levels HbA1c during CSII treatment: 9,77±2,151% (before CSII treatment) vs. 8,65±2,080 (after 1st year of CSII treatment) ($p<0,001$), 8,11±1,635 (after 2nd year), 8,29±1,613 (after 3rd year), 8,36±1,847 (after 4th year), 8,49±1,589 (after 5th year). The control of diabetes during CSII treatment is equal to HbA1c before CSII treatment. At the same time the mean daily insulin dose was reduced: 48,0±18,16 IU/day (before CSII treatment) vs. 39,5±12,51 (after 1st year of CSII treatment) ($p<0,001$), 41,3±14,15 (after 2nd year), 41,6±15,82 (after 3rd year), 42,2±13,65 (after 4th year), 39,6±11,76 (after 5th year). The complications of CSII treatment (infection, ketoacidosis, hypoglycaemia,...) are not frequent and do not lead to CSII treatment termination.

Conclusion: We can declare according of all data that CSII treatment is effective, safety and have well-founded indications. The required data are fully representative with respect to the number of observed diabetic patients and the duration of monitoring (1998 - 2002).

How Rapid Does Glucose Concentration Change in Daily-Life of Patients with Type 1 Diabetes?

Karsten Jungheim[1], Christoph Kapitza[2], Christian B. Djurhuus[3], Klaas J. Wientjes[4], Theodor Koschinsky[5] for the Glucose Monitoring Study Group[6]

[1]Corresponding author/presenter:
German Diabetes Research Institute,
Auf'm Hennekamp 65, 40225 Duesseldorf, GERMANY;
Tel: +4921133821 • Fax: +492113382603
jungheim@ddfi.uni-duesseldorf.de

[2]Profil Institute for Metabolic Research, Hellersbergstrasse 9, 41460 Neuss, GERMANY
Tel: +49213140180 • Fax: +4921314018555
christoph.kapitza@profil-research.de

[3]Kommunehospital Aarhus, Noerrebrogade 44, 8000 Aarhus, DENMARK
Tel: +4589492013 • Fax: +4589492010
cbd@dadlnet.dk

[4]University Center of Pharmacy, Antonius Deusinglaan 1, 9713 Groningen, THE NETHERLANDS
Tel: +31503633284 • Fax: +31503632500
k.c.wientjes@farm.rug.nl

[5]German Diabetes Research Institute, Auf'm Hennekamp 65, 40225 Duesseldorf, GERMANY
Tel: +4921133821 • Fax: +492113382603
koschins@neuss.netsurf.de

[6]Prof. Dr. Michael Berger (Düsseldorf); Prof. Dr. Jens Sandahl Christiansen (Århus/Dänemark); PD Dr. Lutz Heinemann (Neuss); Dr. Cornelia Haug (Ulm); Prof. Dr. Theodor Koschinsky (Düsseldorf); Prof. Dr. Thomas R. Pieber (Graz, Österreich); Prof. Dr. Adelbert Schoonen (Groningen, Niederlande); Prof. Dr. Urban Ungerstedt (Stockholm, Schweden)
Contact: Lutz Heinemann, Profil Institute for Metabolic Research
Hellersbergstrasse 9, 41460 Neuss, GERMANY
Tel: +49213140180 • Fax: +4921314018555
lutz.heinemann@profil-research.de

Clinical-experimental studies showed that at alternative sites (forearm, abdomen) blood glucose (BG) concentration changes can be significantly delayed compared to those at the fingertip if BG-change-velocity exceeds approximately 2(mg/dl)/min. Whether such rapid BG-changes occur in daily-life remained an open question. Therefore, we determined the distribution of the glucose-change-velocity by systematically analyzing continuous glucose profiles.

Glucose profiles were registered under daily-life conditions for up to 4 days in 13 patients with type-1 diabetes [male: 10; 18-57yr; DM-duration:4-37 yr; HbA1c:7.7±0.9%]. Interstitial glucose-concentration was measured minute-by-minute by use of a microdialysis-based subcutaneous continuous glucose monitoring device (Accu-Chek Monitor, Roche Diagnostics/Germany). A calibration based on multiple capillary blood glucose measurements was performed retrospectively. For each recorded minute [t=i], a linear regression analysis was performed over adjacent

(±4min) glucose recordings. Glucose-change-velocity was defined as the slope of the corresponding regression line. It is presented in absolute values, i.e. irrespective of the direction of glucose-change (i.e. glucose-increase=glucose-decrease). Median (range) is given.

A total of 987hr was analyzed, i.e. 73hr/patient (39-94). The distribution of data for glucose-increase and -decrease, respectively, was similar. Intra-individual glucose-change-velocity was 0-1(mg/dl)/min in 80% (69-86), 1-2(mg/dl)/min in 18% (12-25) and ≥2(mg/dl)/min in 3% (0-12)of recorded time. The most rapid recorded glucose-change-velocity was 5.0(mg/dl)/min. In 12/13 patients at least one episode (≥15min) with a glucose-change-velocity of ≥2(mg/dl)/min (median:3.5 episodes/patient; range:1-12) occurred. The individual maximal duration of episodes ≥2(mg/dl)/min these 12 patients ranged from 18-70min (median:36).

Rapid glucose-changes ≥2(mg/dl)/min of clinically relevant duration occurred in almost all patients even though glucose-changes as rapid as this represent just a small fraction of diurnal BG-changes. Therefore, sporadic occurance of a relevant lag in BG-concentration at alternative sites seems likely even in daily-life.

Developing a Comprehensive Computer-Based Community Diabetes Management System at NorthEast Medical Center (NEMC)

Douglas G. Kelling, Jr., MD

Concord Internal & Pulmonary Medicine
200 Medical Park Drive, Suite 550
Concord, NC 28025
Tel: 704-783-1199 • Fax: 704-783-1090
dkelling@northeastmedical.org

Since 1995 NEMC in Concord, NC has been developing a comprehensive diabetes management system using a computer program that was created internally with some third party technical support. The program is guided by protocols developed using ADA evidence-based guidelines. Relevant data such as HgbA1C, blood pressure, lipids, proteinuria, etc. are entered into the database when patients are enrolled and continued in an ongoing basis. Participating physicians have computer access to their patient's data to help risk stratify patients seen in the office. On a regular basis, physicians receive reports summarizing their outcomes in managing risk factors associated with complications of diabetes. Six-year outcomes from one clinic show the percentage of patients with HgbA1Cs less than 7% has increased from 26% to 68%; the percentage of patients with LDL cholesterol less than 100 has increased from 21% to 56%; and the percentage of patients with blood pressure of less than 130/80 has increased from 20% to 47%. A committee consisting of physicians and other healthcare providers oversee the program. They review outcomes and make recommendations for performance improvement. Currently 28 physicians in 10 clinics in our county have approximately 5600 diabetics enrolled in the program. We are continuing to add patients from other physicians and staff at NEMC. Our goal is to enroll all of the patients with diabetes who obtain their primary health care at NEMC. We are also in the process of upgrading our database for end-user access via the Internet so other communities can use our system to set up similar programs.

Quantifying Diabetes: New Methods for Analysis and Mathematical Modeling of Self-Monitoring and Continuous Monitoring Data

Boris P. Kovatchev*, Daniel Cox, Anthony McCall

University of Virginia, Charlottesville, VA

*Corresponding Author
UVA Health System
Box 800137, Charlottesville, VA 22908
Tel: 434-924-8656 • Fax: 434-924-8652
boris@Virginia.edu

A challenge to the clinical optimization of blood glucose (BG) control for both Type 1 and Type 2 diabetes (T1DM, T2DM) is the development of: 1) Technologies monitoring patients' BG fluctuations, and 2) Algorithms for data interpretation in terms of assessment of glycemic control, evaluation of risks for hypoglycemia, and intelligent feedback to the patient. While new self-monitoring and continuous glucose monitoring (SMBG, CGM) technologies are rapidly emerging, the development of diabetes-specific computational methods that analyze the wealth of accumulated data is clearly lagging behind.

In this presentation we discuss two types of analytical strategies that quantify long-term characteristics of diabetes control, such as HbA1c, and long-term risk for severe hypoglycemia (SH), and short-term characteristics, such as imminent risk of moderate/severe hypoglycemia. These strategies take into account the specifics of the BG fluctuations, which: (1) Observed over longer periods of time have nearly random behavior and are therefore analyzed by stochastic/ statistical inference methods, and 2) Observed over short periods of time are nearly deterministic and are analyzed by dynamical models and differential equations.

Specifically we present: (1) The theory and the results from our Risk Analysis of BG data (Low and High BG Indices), including prediction of 50% of upcoming SH episodes, and (2) A nonlinear model of BG dynamics, including idiosyncratic estimates of insulin sensitivity, impaired glucose counterregulation, and risk for immediate hypoglycemia. The first section of this presentation uses routine SMBG data, while the second applies to analysis of CGM data.

We conclude that diabetes-specific computing methods have significant practical/clinical utility.

Acknowledgements: These studies were supported by NIH/NIDDK grant RO1 DK 51562 and by a grant from Lifescan Inc., Milpitas, CA.

Register of Patients Treated by the Insulin Pump based on the Diabcare Basic Information Sheet

R. Kožnarová*, T. Pelikánová, D. Hackajlo, A. Jirkovská and V. Lánská

*Institute for Clinical and Experimental Medicine, Department of Diabetes
Videnska 1958/9, 140 21 Prague 4, Czech Republic
Tel: +4202 6136 3186 • Fax: +4202 6136 2820
radomira.koznarova@medicon.cz

Collection of relevant data is a key process to reach targets of the Saint Vincent Declaration and improve the quality of care. The essential pre-requisite to the accurate measurement of the outcomes are computerized diabetes registers.

The **aim** of the study is to present a register of diabetic patients treated with continuous subcutaneous insulin infusion (CSII) using the insulin pump (IP).

Methods: The data collection was based on the DiabCare Basic Information Sheet extended by data including the reasons for employing the IP and the complications related to the IP treatment.

Results: As of 31 December 2001, the IKEM-based IP-treated patient registry included 323 patients; of this number, 275 were on long-term follow-up. Evaluation was made in a group of 256 IDDM patients who had been treated by the IP for more than 3 months. The mean period of diabetes treatment in the group was 18.7 ± 8.7 years, mean period of IP therapy was 2.93 ± 1.8 years. Most common CSII indications were dawn fenomenon and recurent nocturnal hypoglycemia. The mean daily dose of insulin before IP installation was 51.0 ± 15.3 U, being 42,0±12,5 U at the end of follow-up (p(0.001). The mean HbA1c significantly decreased during follow-up (10.08 ± 2.0% vs. 8.59 ± 1.3%(p < 0.001). The register also includes data on complications related to diabetes treatment: incidence of cannula-based infections, severe hypoglycemias, ketoacidosis, weight gain, and technical complications.

Conclusions: We present the register of IP-treated diabetic patients which serves to assess the quality of care provided to diabetic patients. The results obtained from the register indicate its high efficacy and minimal incidence of therapy-related complications.

Supported by grant

A Wireless, MEMS Fabricated, Continuous, Minimally Invasive, Dermal, Micro-sensor Platform

Albert P. Kretz, Ph.D., M.B.A.[1], Alain Izad, Ph.D., M.B.A.[2], Miklos Gratzl, Ph.D.[3]

[1]Advanced Biosensors Inc., PO Box 385 Mentor, Ohio 44061
(440) 918-9880, (440) 918-9885
info@advancedbiosensors.com

[2]Advanced MicroMachines, Goodrich Corp. 11000 Cedar Ave. #240 Cleveland, Ohio 44106-3052
216-229-4636 ext 201, 216-229-4774
aline.izad@goodrich.com

[3]Dept of Biomedical Engineering
Case Western Reserve University 10900 Euclid Ave. Cleveland, Ohio 44106-7207
216-368-6589, 216-368-4969
mxg13@po.cwru.edu

Micro Electro Mechanical Systems (MEMS) design concepts were used to fabricate a minimally invasive, percutaneous, solid-needle-type, continuous, micro-sensor platform. This device will be used initially for glucose monitoring in animal studies. After FDA clearance, inserted by a patient into non-finger sites, this micro-sensor is expected to reduce the pain and trauma associated with current needle-type devices. The first model, Mark I, can remain in-place for 3 days. A second model, Mark II, incorporating a novel, provisional patent-protected polymer system to create a condition termed "Wound Stasis", will be able to remain in the skin for greater than 3 days. Such a user-friendly micro-sensor can be expected to lead to greater utilization of "tight glucose control" with its associated long-term benefits.

The continuous micro-sensor has potential for exceptional assurance of detecting trends toward low or high blood sugar levels and pending hypo/hyperglycemic events. Providing this information can lead to awareness and timely intervention. Appropriate corrective action can assure maintenance of euglycemia (normal glucose levels).

We report construction of a micro-sized sensor base, 100-200 mm wide and 1-2 mm long. In-vitro tests indicated a nanoamp current proportional to physiological glucose concentrations when immersed in glucose/phosphate buffered saline. The basic micro-sensor design can be applied to other analytes and has capability for multiple analyte measurements. A wireless version will soon be available for use with animals.

With wireless coupling to an appropriately designed, portable insulin pump, this continuous, micro-sensor can lead to realization of an EXTERNAL ARTIFICAL PANCREAS.

Mid Infrared Absobrtion-based Measurement of Glucose in Biological Fluids

S. S. Krishman[1] and J. P. Gore[2]

1003 Chaffee Hall
Maurice J. Zucrow Laboratories
School of Mechanical Engineering
Purdue University
W. Lafayette, IN 47907.

[1]Tel: (765) 496-2849
Fax: (765) 494-0530
kumarsk@ecn.purdue.edu

[2]Corresponding Author
Tel: (765) 494-1452
Fax: (765) 494-0530
gore@ecn.purdue.edu

Simple methods of mid infrared spectral analysis are presented for use in the measurement of glucose in biological fluids. Clinically relevant concentrations (0.05 – 0.5 g/100mL) of glucose dissolved in distilled water and Lactated Ringer's Solution (LRS), human serum samples and rat interstitial ultrafiltrate fluid samples are analyzed. The absorption signals because of glucose are relatively small peaks that modify the absorption spectrum of water. Partial Least Squares (PLS) was used to calibrate and validate the glucose concentration values for the distilled water, LRS, human serum and rat interstitial ultrafiltrate fluid samples. The results of these multivariate calibration methods are described. The results indicate that measurements in the mid infrared give excellent correlation with glucose concentration in the presence of interfering compounds in human biological fluids.

A New Method for Continuous Glucose Monitoring Based on Osmotic Pressure

Helge Kristiansen[1], Baard Kulseng[2]

[1]SINTEF Instrumentation and microelectronics
P.B. 124 Blindern
N-0314 Oslo, Norway
Tel: +47 22 06 75 50
helge.kristiansen@sintef.no

[2]Department of Cancer Research and Molecular Biology
Norwegian University of Science and Technology
Trondheim, Norway

The development of continuous glucose-sensing systems is a potentially important advance in the management of type 1 diabetes. However, until now there has been no glucose sensor available that can be used by diabetic patients in daily life conditions over a sustained period.

We are presently developing a new technique for continuous subcutaneous glucose monitoring based on the fact that the concentration of glucose is an important component to the total osmolality of the body liquid. The concentration of glucose can therefore be indirectly determined by measuring changes in osmolality. This can be done by inserting a device in the patients subcutis, comprising a sensor with an enclosed volume of a calibrated liquid (reference solution) with a body liquid osmolality close to normal. This solution is separated from the body fluids by a semipermeable membrane, through which glucose is not permeable. The difference in osmolality between the reference solution and the subcutaneous interstitial fluid is generating a pressure, measured by a miniaturised silicon pressure sensor. A signal dependent on this pressure is transmitted from the sensor to an outer receiver unit with signal processing, display and memory functions.

By optimising the osmotic membrane combined with techniques, which are under development, for the compensation of osmotic changes caused by other molecules we expect to be able to determine the glucose concentration. Results of in vitro studies shows that we can measure the differences in glucose concentration between reference volume and external liquid with a very high resolution (better than 0,01 milliOsmol).

DiaBetNet: Learning and Predicting Blood Glucose Results to Optimize Glycemic Control

Vikram S. Kumar[1, 3]*, Alexa Connell[2], Ashish Kapoor[3], Daanish Khatri[3], Jesse Lacika[3], Alison Tovar[2], Laura Vangsness[2], Jessica Zuehlke[2], Sandy Pentland[3] PhD, and Lori Laffel[1,2]** MD, MPH

[1] Harvard Medical School
[2] Joslin Diabetes Center
[3] Massachusetts Institute of Technology

*(Presenter)
E 15-384C20 Ames Street, Cambridge MA 02139
Phone: 617-236-4932 • Fax: 617-253-8847kumar@mit.edu

**Joslin Diabetes Center
One Joslin Place, Boston, MA 02215
Phone: 617-732-2603 Fax: 617-732-2451
lori.laffel@joslin.harvard.edu

Blood glucose monitoring (BGM) is critical for optimal glycemic control in type 1 diabetes (T1DM). To better understand BGM behavior in youth with T1DM, we performed a clinical study called DAILY (Daily Automated Intensive Log for Youth) in which we compared usual care with a community-based predictive game (DiaBetNet) aimed at motivating BGM frequency. Forty youth with T1DM, ages 7-18 years, from New England were randomized to Game (DiaBetNet) or Control groups for the four-week pilot study.

Both groups used a wireless-enabled handheld-computer to enter carbohydrate intake and insulin doses and to receive BG data transferred from an IR-enabled Accu-Chek® Active™ glucose meter compatible with Accu-Chek® Pocket Compass™ software (Roche Diagnostics Corporation, Indianapolis, IN). Using the handheld-computer, the children in both groups could wirelessly send their encrypted data to a centralized, secure server.

Once a day, the Game group played DiaBetNet in which they had to predict a future BG level based on a graph depicting the day's earlier BG levels, carbohydrate intake, and insulin doses. To qualify to play, each participant had to check BG levels at least three times. Players earned points for entering carbohydrate intake and insulin doses, transferring BG data, and participating in the day's game. Organized into teams, the children could earn team-points by analyzing data and predicting future BG levels of others.

Based on this study, we are determining whether DiaBetNet will encourage greater frequency of BGM in the Game vs. Control group. Further, we are examining statistical machine learning techniques to analyze how well a person can learn to predict the behaviors of physiologic parameters and whether intelligent machines can enhance understanding for better control of diabetes.

The Delphi Diabetes Registry™ Software Program

Ron Larity, Ginger Kanzer-Lewis

Delphi Health Systems
360 Bloomfield Ave., Windsor, CT 06095
Tel: (860) 687-4704 • Fax (860) 687-4701
rlarity@delphihealth.com
gingerk@csi.com

In collaboration with the American Diabetes Association (ADA), Delphi provides the Delphi Diabetes Registry™ software program to advance the quality of diabetes care. The software is consistent with the ADA Standards of Care, may be used to apply for ADA Provider Recognition and supports the National Standards for Diabetes Self-Management Education.

The Delphi Diabetes Registry software supports physicians and other members of the diabetes care team by fully automating the planning, delivery, management and ongoing quality assessment of patient care. The software produces interactive outcomes analysis for individual medications, classes of medications, educational interventions, and patient monitoring devices. In support of clinical studies, the software enables clinician-designated patient groups and tracking events to be used for population and sub-population outcomes analysis.

Through the use of Delphi-developed software algorithms that automate the creation and implementation of standards-based guidelines, the diabetes clinical team selects the measures, parameters and thresholds that are used to collect, monitor and report the clinical status of all patients. The program assesses the status, measures the progress and reports the results for all patients under care. The program assures the delivery of standards-based, cost-efficient, quality diabetes care -- delivered to the appropriate patient at the appropriate time.

The Registry software analyzes clinical results on an ongoing basis, producing alerts for results above established thresholds, reminders for scheduled tests and visits, and context-sensitive patient communication and education.

The software includes a predictive High-Risk Monitor that stratifies ongoing patient risk based on parameters set by the clinical team. This ongoing high-risk assessment creates an opportunity for earlier identification and intervention before the occurrence of high-expense care episodes.

The Establishment of a Telemedicine Diabetic Retinopathy Surveillance Program in the VHA Upper Midwest Network

Mary G. Lawrence, MD, MPH[1,2,3], Sandra K. Schmunk, BS, MA, HHSA[1], Gary S. Michalec, BS, CRA, COA[2]

[1]VA Upper Midwest Network
[2]Minneapolis VAMC
[3]University of Minnesota, Department of Ophthalmology

Background: Although regular retinal examination is recommended for all diabetics, compliance for this care standard is low.

Purpose: The purpose of this project was to establish and evaluate an innovative diabetic retinopathy surveillance program in a large Veterans Health Affairs (VHA) network using telemedicine technology.

Methods: A program was initiated to have diabetic patients undergo photographic digital imaging along with a brief ocular history, visual acuity measurement and intraocular pressure reading in the same location at which they receive their primary diabetes care. Digital images were sent from the remote site to a "reading center" where ophthalmologists skilled in the evaluation of diabetic retinopathy evaluated the images. Patients who showed evidence of ocular pathology (diabetic retinopathy or other) were referred for confirmatory face-to-face evaluation and possible intervention. The program was evaluated by comparing rates of compliance before and after program initiation. Quality assessments of image "readability" as well as patient and staff satisfaction were also performed. A cost analysis model was also developed.

Results: Compliance with diabetic retinal evaluations improved after implementation of the program. Quality of the transmitted images was adequate with ~22% of patients requiring referral for a face-to-face evaluation. The program received high satisfaction from both patients and staff. The cost analysis model showed the most significant cost variables to be the number of diabetics at each location and the cost of each camera.

Conclusion: Diabetic retinopathy surveillance using photographic telemedicine technology is an effective, efficient alternative to conventional retinal evaluation methods.

Telemonitoring in Diabetes. A New Ubiquitous Service for its Application

Luis Martinez Lebrusant M.D., Medical Director, Croniweb S.A.

Croniweb S.A. Medical Department
Calle Teniente Coronel Noreña, 11, 2°, 28045 - Madrid. Spain
Phone: +34 91 577 71 40 • Fax: +34 91 577 25 64
lmartinez@croniweb.com

The Glucobeep System that we described tries to empower diabetic people in the decision making about its health, to improve their therapeutic compliance and consequently to make possible one more healthful life and of greater quality. It does not try to replace the periodic medical consultations, but rather to facilitate and to maintain the communication between those visits. It is just the solution to common barriers that interfere communication between the health care professionals and their diabetic patients.

The system is composed by a small electronic device for the patient, a dedicated software to installed at the regular PC of the healthcare professional and a server computer with a proprietary software.

The diabetic does not require of any special knowledge, nor need any hardware beyond a simple telephone and the small device, that will be able to copy all data stored in the memory of the blood glucose meter. Most common brands of B.G. Meters are suitable for data downloading. Once data are download, they are transmitted through the telephone line converted into DMFT signal. In addition to all blood glucose meter data, users can send voice messages that complement or clarify these data.

Through the professional software, the data and messages sent by the patients are received, evaluated and answered by means of an Internet access. To evaluate patient data the software friendly allow the use of different statistical tools. The answer to the patient is done using also voice messages.

The Server of the system stores in a safe manner the data and messages sent by the patients, as well as the answers of the professionals and make them available to the other, that will receive them when he/she wishes. In this way the communication neither depend on fixed schedules nor on the physical presence. The use of voice messages gives to the system a touch of personal and customized relation to both patients and doctors or diabetes educators.

Continuous Glucose Quantification by Electrochemical Impedance Measurements on a Concanavalin A-Si/Sio2 Substrate

O. Leloup*[1], A. Macanovic[2], M.F. Lawrence[2], C. Polychronakos^[1]

[1]Department of Pediatrics and Human Genetics
McGill University Health Center (Montreal Children's Hospital)
2300 Tupper street, Montreal, Qc, Canada, H3H 1P3

[2]Department of Chemistry and Biochemistry
Concordia University
1455 de Maisonneuve W., Montreal, Qc, Canada, H3G 1M8

*Presenter
McGill University Health Center, Place Toulon
2300 Tupper, Montreal, Qc, Canada H3H 1P3
Tel. 514 412 4400 ext. 22623
oleloup@hotmail.com

Continuous direct glucose quantification is a highly desirable goal in improving management of diabetes mellitus. Towards the development of a robust non-enzymatic sensor based on reversible binding to the lectin concanavalinA (ConA), we examined whether such binding could be quantitatively detected by its effect on electrochemical impedance of ConA-coated Si/SiO2 substrates. This method has been used to detect non-covalent molecular interactions such as antigen/antibody recognition and DNA hybridization, including precise Tm measurements for the detection of single-nucleotide mismatches. ConA immobilization was achieved by epoxysilane grafting on the silicon layer of the chips, followed by addition of the lectin in a sodium chloride buffer. The duration of the coating reaction of the silane-functionalized chips with ConA was optimized to 90 min as shown in Fig.1, using fluorescent imaging with FITC tagged ConA (Fig. 2) as the end-point. The optimized chips were then used for impedance measurements in a three-electrode design at 50kHz, in a buffer with the ionic composition of extracellular fluid at pH 7.4, in the presence of variable glucose concentrations. A reproducible dose-dependent shift in the impedance/voltage curve was observed (Fig.3). The long term stability of the system is currently under investigation.

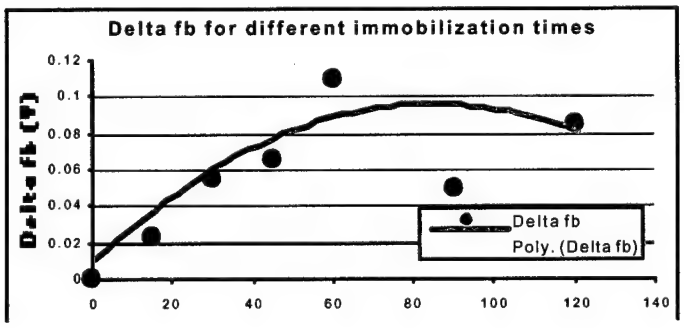


Fig 1. Immobilization time optimization

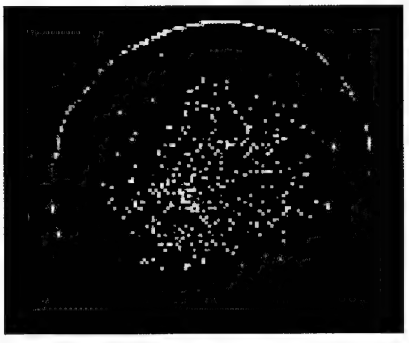
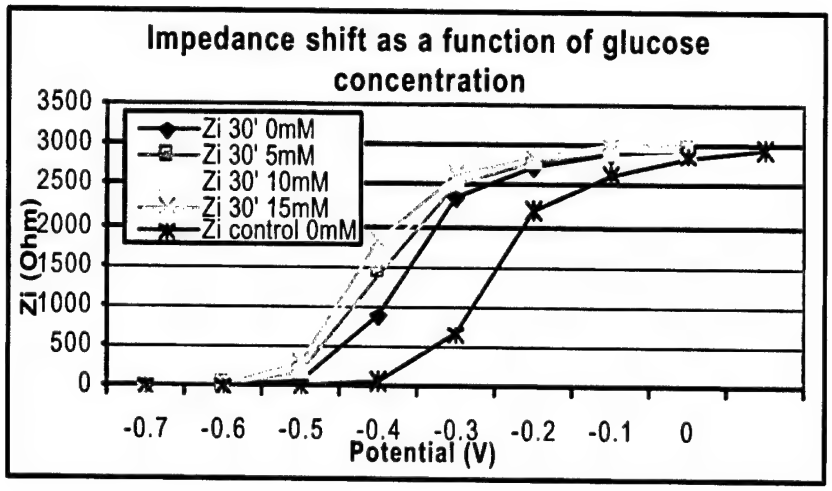


Fig 2. Fluorescent scanning


Impedance shift as a function of glucose concentration
Zi 30' 0mM
Zi 30' 5mM
Zi 30' 10mM
Zi 30' 15mM
Zi control 0mM
Zi (Ohm)
3500
3000
2500
2000
1500
1000
500
0
-0.7
-0.6
-0.5
-0.4
-0.3
-0.2
-0.1
0
Potential (V)

Biotransport and Biocompatibility of Nanoporous Biocapsules for the Encapsulation of Pancreatic Beta Cells

Lara Leoni[1] and Tejal A. Desai[2]

[1]Corresponding/presenting author
Department of BioEngineering, University of Illinois at Chicago
851 S Morgan St. #218, Chicago, IL -60607
Tel: 312 - 413 5208 • Fax: 312-996 5921
lara@uic.edu

[2]Department of Biomedical Engineering, Boston University
44 Cummington St, Boston, MA 02215
Tel: 617 - 358 3054 • Fax: 617-353 6766
tdesai@bu.edu

The mass transport properties of an encapsulation membrane are critical since the influx and outflux of relevant molecules will determine the extent of encapsulated cell viability. At the same time, the membrane must be able to provide considerably greater impedance to the diffusive transport of large molecular weight immunomolecules. In addition, when the device functions as an implantable homeostatic sensor-release system, it is fundamental for the entrapped cells to be able to respond promptly to fluctuations in solute concentrations of the interstitial fluid in order to retain a physiologic dynamic response.

Traditional encapsulation technologies have used polymeric semipermeable membranes. However, a number of challenges remain with these polymeric capsule designs. To overcome some of these limitations we proposed an immunoisolation device based on a microfabricated nanoporous membrane. Utilizing bulk and surface micromachining, membrane-based biocapsules can be engineered to have uniform and well-controlled pore sizes, channel lengths, and surface properties. This precise control offers the unique ability to selectively vary parameters in order to monitor the passage of a variety of stimuli and immunomolecules to target cells.

The diffusion of glucose, albumin, and immunoglobulin G through membranes with pore size ranging from 7 to 49 nm was characterized and found to follow zero-order kinetics. In order to minimize capsule formation and improve the long-term performance of the biocapsule, in vivo polyethylene glycol (PEG) molecules were immobilizated onto the nanofabricated membranes and host's response to the biocapusle was assessed for different implantation sites.

The Affective Factors in Regulating Glycemia and Eating Behavior, an fMRI Study

Yijun Liu and G. Andrew James

Psychiatry and Neuroscience, University of Florida McKnight Brain Institute
100 Newell Drive, L4-100M, Gainesville, FL 32610
Tel: (352) 294-0414 (Office); 392-2573 (Lab) • Fax: (352) 392-2579
http://fmri.mbi.ufl.edu
yijunliu@ufl.edu

Functional magnetic resonance imaging (fMRI) was used to study the central glycemia regulation and its relationship with emotion and over-eating. Affective-cognitive processes yield a strong influence on eating behaviors. The recent neuroimaging finding that merely displaying food can lead to increased dopamine levels in the human brain further confirms the neural substrates of rewarding value of food. The emotionally-laden reward associated with food stimuli shifts feeding from biochemistry based survival behavior to one driven in part by hedonism and societal cues. To further evaluate the importance of affective processes in the control of eating behaviors, we conducted an fMRI study to investigate changes in brain activity with hunger under different emotional challenges. The ventromedial prefrontal cortex (vmpfc), a brain area intimately involved in modulating rewarding behaviors, was significantly more active in hungry subjects in response to food stimuli than animal stimuli that were visually presented with the same arousal effects. In contrast, animal stimuli yielded increased vmpfc activity relative to food stimuli in sated subjects. This dissociation reflects a hunger-dependent shift in the reward value (valence) of food stimuli. The findings are indicative of an affectively driven eating behavior that may be independent of biochemical signaling as measured by blood sampling. Future studies correlating neural activity (including hypothalamic activity) to biochemical or hormonal signaling in both obese people and psychiatric patients will better illustrate the independence or interdependence of affective and biological processes in regulating glycemia in the brain.

Insulin Pump Therapy from Diagnosis of Type-1 Diabetes

N. K. Maclaren*, N. Ramchandani, S. Ten, and A. Kukreja

Weill Medical College of Cornell University, New York, NY 10021

*Cornell Juvenile Diabetes Program
1300 York Ave., Room LC-623, New York, NY 10021
Tel: (212)746-1894 Fax: (212)746-1185
nkm2001@med.cornell.edu
nkmaclaren@aol.com

A growing experience indicates that continuous subcutaneous insulin infusion (CSII) is the best available means of insulin replacement therapy for patients with type-1 diabetes (T1DM). CSII has an improved quality of life compared to that obtainable using multiple daily injections (MDI) and less risk of hypoglycemia. We reasoned that implementation of CSII at time of diagnosis should therefore be evaluated. We have initiated a formal study to test the feasibility and possible metabolic benefits of this approach. Nine pediatric patients (average age = 12.1 years at diagnosis) and one adult patient (61.7 years) were started on Animas insulin pumps within their first month after diagnosis of T1DM. All patients/families were receptive to CSII and proved to be able to learn pump mechanics as well as patients with established T1DM. All have achieved excellent metabolic control without significant hypoglycemia, with blood sugars in the near-normal range thus far (up to 6 months). While this treatment protocol is initially time-intensive for the diabetes team, it eventually becomes time-saving since there are fewer educational requirements thereafter. Furthermore, CSII is anticipated to be cost-effective by decreasing costs associated with hypoglycemic events and diabetes-related hospitalizations. In our 10 patients, good metabolic control has been achieved with modest exogenous insulin requirements, and all have expressed satisfaction with pump therapy. Now that we have shown that CSII is feasible as the initial therapy for T1DM, further studies are required to determine whether there is a significant metabolic and psychosocial benefit from this approach.

Successful Online Education of Prospective Diabetes Camp Counselors

Toree Malasanos MD, Martha Halsey-Lyda RN, Betsy Wood BSN, MPH, Armando Oliva, Bhavin Patel BS, Phyllis Sloyer, MPA, Jay Klein, Andrew Muir MD

Division of Pediatric Endocrinology, University of Florida College of Medicine
POB 100296, Gainesville, FL 32610,
Tel: 352 334-1390 Fax 352 334-1325
malasth@peds.ufl.edu

Hypothesis: Much of the training for diabetes camp counselors could accomplished by completion of educational modules on FITE (Florida Initiative in Telehealth and Education) website, saving hours of time for the health care team.

Background: Previous years of camp had verified the need for intensive training of camp volunteers prior to attending camp. The knowledge required includes treatment and recognition of symptoms of hypoglycemia, techniques for insulin injection, blood glucose and ketone testing. In 2002 the counselors for the Florida diabetes camp were given access to the FITE website and asked to complete pre and posttests along with the modules. The usual "live" orientation was then shortened from 14 hours to 4 hours.

Results: Counselors found the site easy to use, relevant and many had printed information from the website to bring with them to camp. The scores between pre and posttests improved by an average of 15.8%, with a posttest average of 94.75%. The camp director and physicians found the preparation of the counselors to be similar to years in which the 2 day "live" orientation had taken place.

Conclusion: Online diabetes education is useful, not only for families, but also for secondary caregivers with no or little previous knowledge of diabetes care.

Promising Correlation between a Novel Non-invasive and a Conventional Invasive Method of Blood Glucose Determination during a large Modal Day Clinical Study

James R. Mansfield, Andrew Bushmakin, Catherine Carver

Argose Inc.
230 Second Avenue, Waltham, 02451
Phone: 781-672-5604 Fax: 781-890-6566
jmansfield@argose.com

The pain and inconvenience of dealing with blood and/or interstitial fluid associated with skin penetration is a barrier to glucose self-testing for people with diabetes. Strong evidence from the Diabetes Control and Complications Trial (DCCT) that better control of blood glucose will impact long-term complications of diabetes brings a greater need for frequent, accurate knowledge of blood glucose levels. Argose Inc., using a patented blue-light auto-fluorescence technology, has developed a non-invasive system capable of detecting spectral signals from the skin that correlate well with blood glucose levels.

Two clinical experiment types have been used to test the system: a modal day study primarily on older Type 2 diabetics; and a longitudinal study on a young, Type 1 insulin pump user. In one trial, 114 studies were conducted on 24 subjects (22 Type 2 and 2 Type 1 diabetic subjects, overall mean age 66 ± 10 yr, duration of DM 11.5 ± 8.2 yr, HbA1c 7.1 ± 1.0 %) who were studied over a four-week period. The subjects were given a pre-feeding schedule before each of the study visits to create a balanced distribution of blood glucose from 60 to 450 mg/dL. In the other trial, the single subject (female, 21 yr, pump-using Type 1 DM, 15 yr duration) was studied once a day for 9 days, following a careful regimen to obtain a balanced glucose distribution of 150 to 400 mg/dL.

For the large modal day study, the average error was 7.6 %, (using leave-one-visit-out cross validation) across all visits. For the single-subject longitudinal study, the average error was 8.1 %.

These studies show the kind of clinical accuracy that will be necessary in any consumer device and demonstrate feasibility for a non-invasive glucose monitor for home use.

The Importance of Consistent Meal Carbohydrate Estimation on an External, Adaptive Closed Loop Glycemic Control System

Kym Marco, Chris Perkins, Steven Bousamra, Harvey Buck, Paul Galley, James Long, Robin Wagner, Stefan Weinert

Roche Diagnostics
9115 Hague Road, Indianapolis, Indiana, 46250

Technological advancements in continuous glucose measurement and continuous subcutaneous insulin infusion favor the automation of glycemic control with an algorithm-driven closed loop system. To provide clinically acceptable glycemic control with subcutaneous insulin delivery, it is anticipated that the user will notify the system of pending meals. The user will input an estimation of the carbohydrate (CHO) content of the meal to be consumed, thereby notifying the system and driving the algorithm to calculate the appropriate insulin therapy.

Due to the adaptive properties of our algorithm driven system, the ability of the system to provide acceptable glycemic control is dependent upon the consistency of the CHO estimation as input by the user. The primary objective of our research was to assess the consistency with which insulin pump users estimate 1) CHO content of commonly known foods and assign these foods to low, medium or high CHO content categories and 2) the rate at which their blood glucose would increase following consumption into slow, moderate or rapid categories.

Our web based survey of familiar food images with portion descriptions indicates that the 102 insulin pump users studied were best able to consistently estimate the CHO content of foods into low and high carbohydrate categories. However, they exhibited considerable inconsistency in their ability to estimate the CHO content of foods in the medium category, resulting in overlapping category classifications. Implications of this degree of inconsistency to classify carbohydrate content must be considered in the development of an algorithm-driven closed loop system. Further implications prompt exploration into carbohydrate estimation training programs, dietary variety and user input devise design.

Calibration Model of Noninvasive Near-Infrared Monitoring of Blood Glucose

Katsuhiko Maruo, Mitsuhiro Tsurugi, Mamoru Tamura

NBT Project, Matsushita Electric Works, Ltd.
1048, Kadoma, Osaka 571-8686, Japan
Tel: +81-6-6904-4425 Fax: +81-6-6904-6549
maruo@hal.mew.co.jp

For noninvasive near-infrared monitoring of blood glucose, a "universal" calibration model is required to predict the blood glucose levels without pre-examination of subject. However, an individual diversity makes it difficult to formulate a "universal" calibration model. Here, we propose the new calibration method applicable to the universal measurements.

Blood glucose levels were predicted with a particular optical fiber probe by which selective spectral measurements of dermis tissue were possible and the undesired noise originated from stratum corneum was eliminated. The 5 healthy male volunteers with ages from 27 until 47 years were subjected to the examination. Oral glucose tolerance tests were performed for these patients and near-infrared reflectance spectra and blood glucose levels were measured. Partial least square regression analysis (PLSR) was carried out to correlate with these data individually and 5 calibration models were obtained from these patients.

The blood glucose levels of these patients were predicted by substituting spectral data for the other subject's calibration model. From the prediction result these calibration models could be classified into two categories. Among the patients belonging to the same category, the blood glucose levels were predicted in good correlation using other subject's calibration model. However this calibration model did not predict the glucose levels of the subjects belonging to another category. Then, the principal component analysis (PCA) of near-infrared spectra of these subjects was performed. The PCA indicated that the principal factor of the spectra differed clearly between these two categories. It is suggested that the "universal" calibration model cloud be prepared by the classified subjects.

Oral Insulin Delivery Using Bioadhesive Microspheres

Edith Mathiowitz, Stacia Furtado, Danielle Abramson

Brown University
Department of Molecular Pharmacology, Physiology and Biotechnology
Box GB-393, Providence, RI 02912
Phone: 401-863-3171 Fax: 401-863-1753
Edith_Mathiowitz@brown.edu
Stacia_Furtado@brown.edu

The purpose of this work was to see the effect of a single dose of insulin-loaded microspheres injected subcutaneously or administered orally to type I diabetic rats. Insulin-loaded microspheres were fabricated using a novel technique known as PIN. Diabetic rats were anesthetized and then given either a s.c. injection or oral gavage of microspheres. Plasma was collected at pre-determined time-points and assayed for both glucose and insulin levels. Bioavailability of our delivery system was determined as well as the peak drug concentration, time to reach maximum drug concentration, and duration of the plasma-insulin curve. When compared to s.c. unencapsulated insulin, microspheres that were administered s.c. increased the relative bioavailability to 120%. These microspheres also provided insulin levels that were higher in peak concentration, occurred later, and were longer in duration. Oral gavage of microspheres resulted in a relative bioavailability of 20% and a slow decline in plasma glucose levels over time. Our microspheres were capable of achieving a sustained release of insulin into the systemic circulation over several hours, and also increased the relative bioavailability of insulin when injected subcutaneously and administered via oral gavage. We foresee an oral delivery system being available in the future.

Transdermal Oxygen Diffusion from Superoxygenated Aqueous Solution (Preliminary Results)

Terrence McGrath[1], Babs R. Soller, PhD[2], Helen Collette, RN[2], Stephen O. Heard, MD[2], Charles Fox[3]

[1]Chief Operating Officer
Hydron Technologies Inc.
2201 West Sample Road, Bldg. 9, Suite 7B
Pompano Beach, FL 33073
Tel: 954-861-6416 Fax: 954-861-6401
tmcgrath@hydron.com

[2]Department of Surgery, UMass Medical School , Worcester, MA 01655

[3]Hydron Technologies Inc.,
2201 West Sample Road, Bldg. 9, Suite 7B, Pompano Beach, FL 33073

Foot ulcers are a frequent diabetic complication leading to 55,000 amputations/year. Ulcers are slow to heal in the diabetic patient in part, because of compromised peripheral oxygen delivery. This study evaluated a new method for delivering oxygen to the skin.

Methods: Ten healthy subjects had a 0.5 mm fiber optic oxygen and temperature sensor (Diametrics Medical, Inc.) placed in the left calf, 1 - 2 mm beneath the skin surface. Holes made for insertion were covered with a water impermeable dressing. After a 1 hour stabilization period the leg was placed in a constant temperature whirlpool bath of deionized water for 30 minutes. The water was then oxygenated to 1100 mm Hg using microbubble technology (Hydron Technologies, Inc.). Dermal PO2 was monitored for an additional 30 min with the leg in oxygenated water.

Results: Baseline dermal PO2 was 31 ± 4 mm Hg. At the end of the control period dermal PO2 was 29 ± 4 mm Hg. After immersion in the superoxygenated water dermal PO2 increased significantly to 44 ± 7 mm Hg ($p = 0.02$). On average there was a 54% increase in dermal PO2 as a result of the treatment, however 2 subjects experienced greater than 125% increase in skin oxygenation.

Conclusions: Superoxygenated aqueous solutions were effective in increasing dermal PO2 levels in this preliminary study of healthy subjects. Several factors may affect the magnitude of dermal oxygenation such as temperature, solution oxygen concentration and skin permeability, requiring further investigation.

This study was funded by Hydron Technologies, Inc.

Evaluation of Risk Factors in the Development of Posttransplant Diabetes Mellitus

Sherri L. Meyer, MS, RD, Carolyn Cochran, MS, RD, CDE, Miguel Vasquez, MD, Barbara Foster, Ph.D., Victorine Imhran, Ph.D., RD, Nichole Wilkerson, MS, RD

968 St Charles Ave # 107, Atlanta, GA 30306
Tel: 404.872.1965 Fax: 404.872.1965
tmeyer@wans.net

Renal transplant has been shown to improve patient survival as well as quality of life. However, renal transplant is not without complications, specifically diabetes mellitus. The purpose of this study was to establish a predictive index using univariate and multivariate analysis to evaluate multiple factors involved in the development of posttransplant diabetes mellitus (PTDM). One hundred and sixteen medical records from various renal transplant centers were evaluated. Qualified subjects were divided into two groups (diagnostic and non-diagnostic). A statistical significance was found between the diagnostic group and pre-transplant blood glucose (BG) ($p=0.028$), pre-transplant body mass index (BMI ($p=0.040$), family history of DM ($p=0.050$), family history severity score ($p=0.008$), HLA type B49 ($p=0.048$) HLA type DR1 ($p=0.018$). Significant univariate predictors were submitted to a stepwise logistic regression technique. The final model consisted of those variables having the strongest relationship with the outcome (pre-transplant BMI, pre-transplant BG, family history severity score and HLA type DR 1.)

Using the model equation, the sensitivity of the tool was only 47.1 %. Thus, over 50 % of persons who may have developed PTDM would have been missed. Though this study did not develop a model that can accurately predict PTDM in the clinical setting, it did identify many risk factors for the development of PTDM. A future prospective study could minimize many of the problems encountered in this retrospective research.

Update on the Long Term Sensor System (LTSS)

Michael Miller[1]*, Rajiv Shah[1], Bahar Reghabi[1], Yanan Zhang[1], Eric Renard[2], Marianne Kollop[1], Nancy Rikalo[3], Lois Jovanovich[3]

[1]Medtronic MiniMed; Northridge, CA
[2]Lapeyronie Hospital; Montpelier France
[3]Sansum Medical Research Institute; Santa Barbara, CA

*Medtronic MiniMed
18000 Devonshire Street, Northridge, CA 91325-1219
(818) 576-5787 (818) 362-5958
Mike.Miller@MiniMed.com

A fully implanted platform for a biomechanical pancreas or an artificial b-cell has been developed by connecting an intravascular glucose sensor to an implantable pump (Medtronic MiniMed 2007B). The combination of sensor and pump or Long Term Sensor System (LTSS) has been implanted in 18 patients in three clinical sites.

Accuracy of the sensor was assessed by comparing sensor output to a standard home glucose meter, either a Lifescan One-Touch or an Accucheck Complete. The study participants were required to measure capillary blood glucose at least six times a day. The LTSS performs a weekly accuracy check based on a single daily meter measurement. This accuracy check controls an as needed calibration scheme, making all calculated glucose prospective in nature rather than retrospective. The LTSS has been implanted in patients for a total of over 7 patient years, in ranges of 56 to 430 days. A total of over 17,000-paired samples were gathered and analyzed. Overall Mean Absolute Deviation (MAD) was 18.71% with 96.6% of these sampled points in the A and B region of the Clarke Error grid. Correlations of these points resulted in an r = 0.8007 to 0.9543.

The LTSS was used as an artificial pancreas on four patients, where the glucose signal from the sensor controlled insulin delivery from the pump. A "closed loop" algorithm was downloaded on demand to the LTSS through a RF telemetry link. The hypoglycemic (<70 mg/dl) glucose distribution and the hyperglycemic (>240 mg/dl) distributions were reduced in three of the patients in the closed loop study. Control in one of the patients was compromised due to high levels of insulin antibodies.

Insulin Delivery by Jet Injections: Mechanisms of Jet Penetration

Samir Mitragotri and Joy Schramm

Department of Chemical Engineering, University of California, Santa Barbara, CA 93106
Phone: 805-893-7532, Fax: 805-893-4731
samir@engineering.ucsb.edu

Pressure-driven liquid jets have been used for intradermal delivery of insulin for many years. In spite of their introduction into clinical medicine, variability and occasional bruising have limited their widespread acceptance. Although numerous clinical studies of jet injectors have been reported in the literature, surprisingly little is known about the mechanisms of jet penetration into the skin. In this study, we report results of our studies aimed at determining the mechanism of jet penetration into the skin. Dermal penetration of jets possessing a range of diameters from 76 mm to 559 mm and a range of velocities from 80 m/s to 190 m/s was studied. Penetration was quantified using radiolabeled drugs. Pressure and velocity of the jets were measured using a calibrated pressure transducer and high-speed photography. High-speed photography was also performed to evaluate the detailed mechanism of jet penetration. Emphasis was placed on understanding the origin of the variability observed in jet penetration into the skin. Results of these studies will be presented.

Novel Intestinal Patches for Oral Insulin Delivery

Samir Mitragotri and Zancong Shen

Department of Chemical Engineering, University of California, Santa Barbara, CA 93106
Phone: 805-893-7532, Fax: 805-893-4731, Email: samir@engineering.ucsb.edu

A novel strategy based on intestinal patches is described for oral delivery of insulin. In this method, millimeter-sized multi-layered patches are delivered in the intestine, where they adhere to the intestine due to the mucosdhesive characteristics of the patches. The patches then release insulin into the intestinal membrane. Release of insulin back into intestinal lumen is minimized by the presence of a low-permeability polymer layer on the backside of the patch. The intestinal patches were prepared by compressing a mixture of a mucoadhesive hydrogel and insulin into a thin cylindrical disk (400 micron thick and 2 mm wide). The patches were coated with a ~50 micron thick layer of a poorly permeable polymer on all sides except one flat face of the disk. These patches adhered well to the intestine with an average force of detachment of about 3 N/cm2. In vivo experiments were performed to assess the ability of these patches to deliver insulin. The results of these studies will be presented. This method offers several advantages for inulin delivery. Specifically, the patches offer high surface area per unit mass of the patch, thereby increasing their adhesion on the intestinal wall. Adhesion of patches on the wall also localizes insulin near the wall thereby offering increased concentration gradient for its transport. The protective layer minimizes insulin loss into the intestine, thereby forcing the drug to diffuse towards the intestinal wall. Furthermore, this layer also minimizes enzyme penetration into the patch, thereby offering protection for polypeptides drugs like insulin.

Transdermal Glucose Monitoring and Drug Delivery by Low-Frequency Sonophoresis

Samir Mitragotri and Ahmet Tezel

Department of Chemical Engineering
University of California, Santa Barbara
Room 3332, Engineering II, Santa Barbara, CA 93106
Tel: 805-893-7532 Fax: 805-893-4731
samir@engineering.ucsb.edu

Low-frequency sonophoresis (LFS) is a non-invasive method of transdermal drug delivery and diagnostics. In this method, a short application of ultrasound is used to permeabilize skin for a prolonged period of time. During this period, ultrasonically permeabilized skin maybe used as a permeable interface to the body. This interface may be used for extraction of analytes or delivery of drugs. The main objective of this study is to understand the mechanisms of skin permeability due to LFS. Although the principal mechanism of LFS is known to be cavitation, little is known about how cavitation actually enhances skin permeability. We are specifically interested in understanding the interactions of cavitation bubbles with the skin surface. We are also interested in assessing the structural alterations in the skin induced by ultrasound. Passive delivery of hydrophilic permeants is believed to occur through the defects (imperfections) in the skin. We hypothesize that LFS, due to cavitation, could be generating more of these already existing imperfections resulting with enhanced delivery of large hydrophilic solutes such as proteins (e.g. insulin). In this study we sought to determine the transport pathways created by low-frequency ultrasound.

Oral Buccal Delivery of Insulin using RapidMist Aerosolized Spray Formulation

Pankaj Modi, Ph.D., MBA

Generex Biotechnology Corp
33 Harbour Square, Suite 202
Toronto, Ontario, Canada M5J 2G2
Tel: 416-364-2551 ext. 246 Fax: 416-364-9363
pankajmodi@aol.com
pmodi@generex.com
c.c. lritacca@generex.com

The inability of subcutaneous (sc) insulin administration to effectively, safely and painlessly control post-prandial glucose levels has encouraged the exploration of alternate methods of insulin delivery. Recently, a novel drug delivery system, based on a unique liquid aerosol formulation, has been developed. This system allows precise insulin dose delivery via a simple, cosmetically acceptable metered dose inhaler in the form of fine aerosolized droplets directed in the mouth, without the pain of a needle. The system introduces a fine-particle aerosol at high velocity into the patient's breath; the mouth deposition is dramatically increased compared with conventional technology. This oral aerosol formulation is rapidly absorbed through the buccal mucosal lining and in the oropharynx regions, and it provides the plasma insulin levels necessary to control post-prandial glucose rise in diabetic patients. This novel, pain-free, oral insulin formulation has a critical series of attributes: rapid absorption, a simple (user-friendly) administration technique, precise dosing control (comparable to injection within one unit), bolus delivery of drug, and room temperature stability. A simplified means for prandial insulin delivery, such as that offered by this technique, will significantly reduce the incidence of key complications by allowing increased patient compliance for consistent drug administration in order to regulate patients' blood glucose levels. This presentation will outline briefly the recent long-term and short-term clinical trials results in Type-1 and Type-2 diabetic patients in comparison to s.c. injected insulin.

Non-Invasive Glucose Monitoring During Dynamic Glucose Condition

Emanuel Monashkin[1], Boris Fikhte[1], Ilya Fine[1], Avraham Karasik[2]

[1]OrSense Ltd. Rehovot, Israel
[2]Sheba Medical Center, Israel

OrSense Ltd.
2 Bergman St., Rabin Science Park
Rehovot, Israel
Tel: +972-8-946 5142 Fax: +972-8-946 5502
orsense@orsense.co.il

This study was conducted to evaluate the new instrument developed by OrSense for non-invasive blood glucose (BG) measurement that utilizes the novel technology of Red-Near InfraRed Occlusion Spectroscopy (RNIR-OS), in comparison with a standard glucometer.

The aim of the trials was to determine the precision level of the non-invasive technology on patients with DM during daily wide dynamic ranges resulting from Meal Tolerance Test.

Methods: Five patients with T1DM of both genders (2 female / 3 male), ranging from ages 23 to 52 years old were admitted.

The patients arrived after overnight fasting and had taken no morning insulin injections. Intravenous access was maintained to allow for collection of blood samples, thus invasive determination of glucose levels could be made concurrently with every non-invasive reading.

Upon completion of baseline BG testing, patients were fed a "sustacal" pudding (5 oz.). Whole-blood samples were drawn at 15-20 minute intervals immediately followed by non-invasive measurements for the next 6 hours. Two hours after the meal, patients resumed their insulin injection. At 2.5 hours after the meal, the patients were given a snack and fruit. 4.5 hours after the meal, the patients received lunch made of carbohydrates and a glass of juice. Sampling and non-invasive measurements were terminated 1 hour after lunch.

Each subject participated for five consecutive day sessions.

One week later, patients participated in five consecutive days of follow-up (non-fasting) BG testing where blood was drawn from the fingertip.

Calibration coefficients were calculated at the beginning of each session (2 measurements) and utilized to compute test results.

In a typical patient, BG range was (50-350 mg/dl), correlation (r=0.86) and mean error (26 mg/dl). See Fig. 1

The study demonstrated that RNIR-OS system can be non-invasively determined in a single subject by daily calibration model of 2 tests.

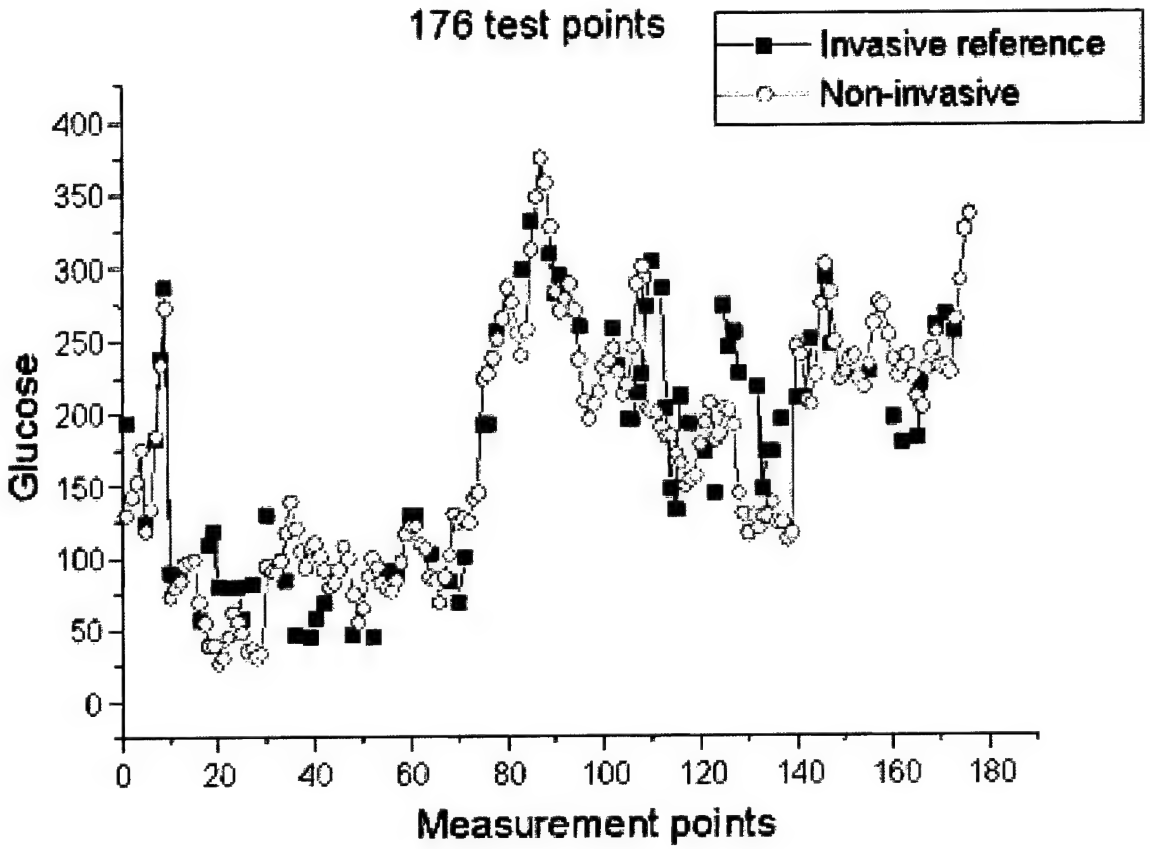

176 test points
Invasive reference
Non-invasive
Glucose
400
350
300
250
200
150
100
50
0
0
20
40
60
80
100
120
140
160
180
Measurement points

Fig. 1

Calcium Phophate-Peg-Insulin-Casein (Capic) Particles as Oral Insulin Delivery System in Diabetic Mice

Tülin Morçöl[1]*, Peri Nagappan[2], Larry Nerenbaum[1], Lucila Garcia-Contreras[3], Qing Hel, and Steve J.D. Belll

[1]BioSante Pharmaceuticals Inc., Smyrna, GA
[2]Department of Anatomy, Morehouse School of Medicine, Atlanta, GA
[3]School of Pharmacy, University of North Carolina, Chapel Hill, NC

*BioSante Pharmaceuticals, Inc.
4600 Highlands Pkwy., Smyrna, GA 30082
Tel: (770) 805-9769 • Fax: (770) 805-9789 (Fax)
tmorcol@biosantepharma.com

Previously we demonstrated the therapeutic effectiveness of proprietary calcium phosphate (CAP) particles containing insulin (Ins) and polyethylene glycol (PEG) as a pulmonary delivery system for insulin in diabetic mice. In this study, the CAP-PEG-Ins (CAPI) particles were complexed with caseins to produce the CAPIC oral insulin delivery system. CAPIC was evaluated in fasted diabetic mice. A single dose of 100 U/kg CAPIC suspension was administered orally. Identical doses of insulin solution and CAPI suspension were used as controls. Blood glucose and serum insulin levels were monitored every 0.5-2 hrs for 10 hours to assess the glycemic effect of CAPIC versus controls.

Following the oral administration of 100 U/kg CAPIC, fasted glucose levels were reduced by 60%-80% within 1-2 hrs of the treatment, which were maintained for 10 hrs. Conversely, insulin solution alone reduced the glucose levels by only 25% within the first 30 min-1 hr of the treatment then returned to control levels in 4 hrs. In animals treated with CAPIC, serum insulin levels increased by 60-fold within the first 1 hr of the treatment and remained 8-fold higher for 10 hrs. Conversely, in animals treated with either CAPI or insulin solution, there was only a 4-fold increase in serum insulin levels which returned to the baseline level in 1 hr.

Our results indicate that the biological activity of insulin is preserved in CAPIC and that the CAPIC formulation has the potential to allow for effective oral delivery of insulin and other therapeutic proteins. Pharmacokinetic analysis of data is currently underway and will also be presented.

NextJen: a Joslin-Developed, Diabetes-Specific Electronic Medical Record (EMR)

A Moses, L Kimker, K Snow, B Hyatt, J Holtshlag, A Principe

One Joslin Place, Boston, MA 02215
617-732-2501
alan.moses@joslin.harvard.edu

Diabetes practice requires the interface of patient information with devices that range from those that acquire data to those that synthesize data. Electronic medical records (EMRs) have simplified some aspects of medical management, however elements specific to a diabetes practice often are not addressed. In an effort to utilize information technology to simplify and standardize care delivery, to allow efficient practice management, and to provide a reliable database for outcomes and clinical research, the Joslin Diabetes Center acquired a standard electronic medical record, NextGen® from Micromed, and customized it to provide a diabetes-specific EMR. This EMR, a relational SQL database named NextJen, has been designed to incorporate the flow of information essential to diabetes management and to facilitate the interaction and collaboration of multiple caregivers. Templates allow for the development of complex insulin treatment regimens and for the cataloging of diabetes complications. Alerts prompt providers about specific clinical issues. Electronic interface between the clinical laboratory and the provider speeds clinical decision making. Direct faxing of prescriptions to pharmacies and of data on medical encounters to referring physicians improves the accuracy of medical care, has the potential to reduce medical errors, and enhances coordination of care. We anticipate that "dumping" of data from blood glucose monitoring devices into a patient's medical record either directly or through distant websites will trigger alerts to providers to review data and take appropriate action. As data from 15,000 active Joslin patients are incorporated completely into the system, the ability to perform outcomes research and to understand and manage the complex practice will be greatly facilitated.

Improved Patient Outcomes Thanks to Medical Genomics: The Case of Diabetic Nephropathy in White and Black Men

David W. Moskowitz, MD, MA(Oxon.), FACP

GenoMed, Inc.
4560 Clayton Ave., St. Louis, MO 63110
Tel: 314-977-0110 Fax: 928-395-2580
dwmoskowitz@genomedics.com
http://www.genomedics.com

Populations from two indigent care St. Louis hospitals (n=6,414) and a southeastern US hemodialysis company (n=3,959) were genotyped for the ACE insertion/deletion (I/D) polymorphism. The ACE D/D genotype frequency was elevated in patients with NIDDM and its complications, as well as many other common diseases, which explains why prevention of NIDDM was observed in the HOPE study. Since the ACE D/D genotype is associated with elevated tissue ACE activity, and since conventional therapy of diabetic nephropathy with ACE inhibitors is disappointing, a novel treatment method using a higher than conventional dose of a hydrophobic ACE inhibitor was designed. A second agent (Florinef®) was often required to treat hyperkalemia due to Type IV RTA, which is exacerbated by ACE inhibitors. This treatment regimen was used for 1,000 male diabetic, hypertensive, and chronic renal failure outpatients over a 3-year period. Diabetic nephropathy could be reversed for white and black male patients with a serum creatinine less than or equal to 2 mg/dl, and significantly delayed for patients with serum creatinine between 2 and 3 mg/dl. Interestingly, black male patients with diabetic nephropathy responded better than white male patients. There were no adverse events specific to this treatment regimen. These results suggest that: 1) prevention of diabetes and its complications is possible once disease-predisposition genotypes are known; 2) to be maximally effective, prevention must begin as early as possible in the course of disease; 3) medical genomics will abruptly change medicine from treating diseases to treating risks; 4) prevention will largely be administered by primary care providers (PCPs). A program of ongoing education in medical genomics and certification in this treatment regimen has been devised and is available.

A Simulation of Glucose Metabolism for Type 1 Diabetes Based on Neural Networks and Compartmental Models

S.G. Mougiakakou*, K.S. Nikita

*Faculty of Electrical and Computer Engineering, National Technical University of Athens,
9, Iroon Polytechniou, Zographou 15 773, Athens, Greece
Tel: +30 10 772 2285 Fax: +30 10 772 3557
smougia@cc.ece.ntua.gr

A hybrid system based on the combination of Compartmental Models (CM) and Artificial Neural Networks (ANN) is presented. The system is able to handle day-to-day data, commonly written in a dairy, from Type 1 diabetes in order to predict short-term blood glucose levels. The prediction is produced by simulating both the external (insulin intake, food) and the internal (liver, gut, insulin dependent glucose utilization, insulin independent insulin utilization) factors influencing the blood glucose profile.

Usually Type 1 diabetes patients record their blood glucose measurements, the insulin doses, and the food intake of a maximum of four times per day. Since this frequency is not enough for the development of a glucose metabolism simulation, a CM is used to refine the patients records with a 15min time resolution. The refined patients records are then fed to an ANN, able to handle delayed inputs, in order to predict subsequent blood glucose values. The system is implemented using data from one Type 1 diabetes patient recording blood glucose level, insulin doses, and food intake for a period of 70 days.

This approach aims to the development of an accurate system for the modeling of glucose metabolism. The system can assist Type 1 diabetes patients to handle their blood glucose profile, and recognize dangerous metabolic states, using only the basic information that is necessarily written in their diary. Alternatively, the system can be extended in the management of insulin dose and meal, which means that it can be used as a decision support system. Finally, such a system could be used for educational purposes not only by Type 1 diabetes patients but also by medical students.

Technology-Based Diabetes Disease Management: A Low-Cost, High-Value Solution for the Management of Diabetes

Pieter Muntendam, M.D.

Kelle Straw
Landacorp
4151 Ashford Dunwoody Road, Atlanta, GA 30319
Tel: 404-531-9956 Fax: 404-531-4826

Background: Although information technology is now a part of all disease management programs, most programs are designed around incorporating only extensive nurse interventions.

Objective: To present clinical and financial outcomes data from One Health Plans technology-based program, CareResultssm, developed by Landacorp, Inc., which provides this care management program to over 60,000 participants with diabetes.

Methods: Data from the health plan's medical and pharmaceutical claims were used to identify the diabetic patient population. The programs use mail, Internet and Interactive Voice Response (IVR) services to engage and motivate the participants.

Patient engagement consisted of an introductory mailing supported by follow-up mailings and phone calls. The CareResults program uses participant reported information to risk stratify the population and to track patients' progress as part of the measurements of the program's results. The risk stratification algorithm scores the participant's clinical status and ability to self-manage their care. Both dimensions impact the participant's risk score, which, in turn, determines the follow-up activities. CareResults mails a personalized feedback booklet as part of a care kit to educate the participant on the current treatment guidelines. The goal is to help participants manage their own care by recognizing good healthcare and teaching them the "language of care." This allows them to more effectively communicate with their physicians and improve their clinical outcomes.

Results: The program demonstrates that improved outcomes can be rapidly achieved for a large number of participants in a cost-effective manner. One Health Plan has identified and provided this care management program to over 60,000 diabetic members in the past two years.

Improved clinical outcomes were demonstrated including a 55.2% increase in receiving glycosylated hemoglobin A1c testing, while financial analysis indicates the program's per member per year net savings was $900.

Effect of Composition and Purity of Alginate on Microcapsule Shape and Size

Emmanuel C. Opara*, William F. Kendall Jr, Marcus D. Darrabie, Hesham El-Shewy, Bradley H. Collins

Duke University Medical Center, Durham, NC 27710

*Corresponding Author
Box 3065, Durham, NC 27710
Tel: 919-684-4120 • Fax: 919-681-7339
opara001@mc.duke.edu

Alginate is commonly used to microencapsulate islets for therapeutic experiments in type I diabetes. Imperfections in the spherical shape, impurities in the microcapsules, and large capsules may contribute to graft failure. The purpose of the present study is to determine the effects of alginate composition and purity, on the morphology and size of microcapsules. Alginate preparations of different chemical composition, viscosity, and purity were obtained. Microcapsules produced with impure medium viscosity guluronic acid (IMVG), low viscosity guluronic (ILVG), low viscosity mannuronic (ILVM), and medium viscosity mannuronic (IMVM) alginate were compared with highly purified low viscosity mannuronic (HPLVM) alginate. Droplets of 1.5% alginate were generated with a 2-channel air jet microencapsulator, and gelled in a 1.1% CaCl2 solution. While leaving the alginate pressure and needle recess constant, we varied the air-jacket pressure between 9.5 PPSI and 10.5 PPSI and made different batches of capsules from each alginate grade. We then assessed the shape and diameters of each batch. Microcapsules of guluronic-rich alginate were consistently bigger than those of mannuronic grade. For example at an air-jacket pressure of 9.0 PPSI, the mean diameter of the IMVG capsules was 780 ± 20 μ, while the IMVM mean capsule diameter was 607 ± 44 μ ($p < 0.0001$, $n = 30$). Similarly, ILVG mean capsule diameter was 816 ± 28 μ, while that of ILVM capsules was 656 ± 26 μ ($p < 0.0001$, $n = 30$). Although, we found that HPLVM capsule mean diameter was comparable to ILVM mean diameter, there was significantly less polymorphism with the HPLVM capsules. The data suggests that utilizing highly purified mannuronic-rich alginate will provide smaller, spherical microcapsules suitable for islet cell transplantation.

Assessment of the Linearity of Subcutaneous Insulin Delivery During Rapidly Changing Insulin Dynamics

Antonios E Panteleon*, Natalie Kurtz, Gayane Voskanyan, Garry M Steil, and Kerstin Rebrin

*Glucose Sensor R&D, Medtronic MiniMed
18000 Devonshire Ave, Northridge, CA, 91325, United States
Phone: (818) 5765281 Fax: (818) 5766206
AntoniosP@minimed.com

Linearity of insulin kinetics is of paramount importance to the design of a closed loop glucose control system, as it allows the plasma insulin pattern for arbitrary infusions to be predicted using the known bolus response. In the present study, linearity of subcutaneous delivery of Lispro insulin was assessed by comparison (N=5) of plasma insulin profiles during a standard euglycemic hyperinsulinemic clamp (3.3 mU/min/kg subcutaneously) with the predicted plasma insulin profile based upon a subcutaneous bolus injection (0.4 U/kg). Insulin was administered in the lateral abdominal area and blood samples were drawn according to a predetermined sampling schedule. A Medtronic MiniMed 506 pump was used for all infusions while injections were conducted with a Hamilton syringe. During all experiments, glucose was infused at a variable rate to maintain euglycemia (~90 mg/dl).

Insulin clearance was not significantly different between the injection and infusion (845.6 ±95.1 ml/min vs. 732.2±30.5 ml/min, P=0.41), suggesting a linear dose response. Nonetheless, comparison of the actual plasma insulin profile after subcutaneous insulin infusion with the expected plasma insulin pattern under assumption of linearity (acquired after convolution of the infusion pattern with the plasma insulin concentration after the bolus) shows that the system deviates from linearity (see Figure). Prolonged Lispro insulin infusion results in a ~40 min transport lag on the falling edge of the plasma insulin concentration.

We conclude that a linear dose response does not necessarily imply a linear dynamic response. We also suggest that extended subcutaneous insulin infusion might induce a transport lag in the subcutaneous absorption, albeit not affecting peripheral insulin clearance.

Development of a Tissue Based Bioluminescent Sensor for Glucose Monitoring and Control

Stacey Patterson[1]*, Rakesh Gupta[1], Hebe Dionisi[1], Steven Ripp[1], Michael Simpson[2,3] and Gary Sayler[1]

[1]Center for Environmental Biotechnology, University of Tennessee, Knoxville, TN

[2]Department of Materials Science, University of Tennessee, Knoxville, TN

[3]Oak Ridge National Laboratory, Oak Ridge, TN

*Center for Environmental Biotechnology
676 Dabney Hall, University of Tennessee, Knoxville, TN 37996
(865) 974-8080
sswiger@utk.edu

Control of blood glucose levels is required for effective management of diabetes. Due to the inconvenience associated with finger stick monitoring, most diabetic patients maintain inadequate self-monitoring regimens. Consequently, normal blood glucose levels are not preserved and diabetes related complications rapidly progress. Therefore, the development of glucose sensors able to automatically respond to hypo- and hyperglycemic episodes through a closed loop insulin delivery system is needed. Bioluminescent bioreporters are whole-cell sensors capable of rapidly and quantitatively measuring various target analytes via the production of visible light. Of the various bioreporter systems available, only the bacterial luciferase system, lux, is capable of autonomous light generation, making it ideal for the development of a continuous, automated glucose sensor. Although the expression of lux to this point has been limited to prokaryotic systems, we have recently expressed the lux system in the yeast, Saccharomyces cerevisiae. Bioluminescence exceeded 4 X 106 photons/second/OD, which is similar to prokaryotic expression. In human cells however, bioluminescence has been modest, ranging from background to 3.5 X 103 photons/second. To optimize expression, we have "humanized" the lux genes at the codon level by introducing silent mutations. Preliminary results using rabbit reticulocyte lysates have shown a seven-fold increase in protein expression of the "humanized" versus the wild-type genes. These results are promising for the potential enhanced in vivo expression of these genes in mammalian cells. Future plans include linking the "humanized" genes to glucose inducible promoters, which will generate a continuous, autonomous bioreporter for quantitative measurement of glucose concentrations. Subsequent fixation of these bioreporters onto integrated circuit optical transducers will result in an implantable biochip capable of continuous real-time glucose sensing and insulin delivery control.

A minigene encoding for GLP-1 provides a novel approach to the gene therapy of diabetes

Riccardo Perfetti* and Hongxiang Hui

*Diabetes Research Laboratory, Anna & Max Webb and Family Outpatient Diabetes Center
Endocrine Training Program, Cedars-Sinai Medical Center
8723 Alden Drive, SSB 290, Los Angeles, CA 90048
Tel: (310) 423-2435 Fax: (310) 423-0429
perfettir@cshs.org

Glucagon-like peptide-1 (GLP-1) is an incretin hormone derived from the proglucagon gene, capable of regulating the transcription of the three major genes that determine the pancreatic b-cell-specific phenotype: insulin, GLUT-2 and glucokinase. The aim of this study was to investigate the potential role of GLP-1 for the gene therapy of a glucose-insensitive pancreatic b-cells. We transfected mouse insulinoma (MIN-6) cells with a DNA fragment of the human proglucagon gene containing the nucleotide sequence encoding for human GLP-1, but lacking the coding region for glucagon. Two constructs were generated: in one of them, the expression of GLP-1 was under the control of the CMV promoter (CMV/GLP-1), while the second was regulated by the rat insulin II promoter (RIP/GLP-1). Northern blot, HPLC and RIA analyses confirmed that the minigene was transcribed, and the protein appropriately translated, processed and secreted in the extracellular environment. Gene expression studies revealed that while CMV/GLP-1 cells did not gain a greater glucose sensitivity as a result of the transfection with GLP-1 when compared to cells transfected with the plasmid alone, RIP/GLP-1 were capable of regulating the gene expression of insulin and GLP-1 based on the concentration of glucose in the culture medium. Detection of the counterpart proteins (insulin and GLP-1) in the culture medium paralleled the observation derived from the northern blot analysis. GLP-1 action was mediated by an IDX-1-dependent transactivation of the endogenous insulin promoter, as demonstrated by gel shift analysis. This was further suggested by a significant increase of the glucose-dependent binding of IDX-1 to the insulin promoter in RIP/GLP-1 cells, but not in CMV/GLP-1 cells or control cells. Finally, we observed that while the GLP-1-dependent secretion of insulin was mediated by an increase in cAMP levels, the transcription of the insulin gene, in response to GLP-1, was in large part cAMP-independent.

Anatomy of a Comprehensive Diabetes Management Program

Joan Perkins and Gwen Hosey

JVN Team
Beetham Eye Institute, Joslin Diabetes Center
One Joslin Place, Boston, MA 02215
Tel: 617 732-2400 X4811 Fax: 617 264-2776

The quest to develop a Comprehensive Diabetes Management Program (CDMP) came about because a consortium of healthcare agencies - Joslin Diabetes Center (via the Joslin Vision Network Eye Health Care program), the Department of Defense (Diabetes Institute and Telemedicine directorate), the Veterans Administration, the Indian Health Service, and the Centers for Disease Control - could not find an application that met the following criteria:

- Web based
- Able to "interpret" host system clinical data
- Modular
- Patient focused
- Designed for care providers at all levels, but aimed primarily NPs, RNs, CDEs, PAs
- Useful in urban, rural, and remote sites
- Unifying the often-fragmented critical aspects of diabetes care: Risk Assessment, care planning, targeted education, and continuous communication.

Why such a massive undertaking? There was critical concern that most applications in the e-Health arena are vertical, with little or no communication between them. This consortium needs a fully-integrated package.
This CDMP is care manager-centric, interactive, based on practice guidelines, and provides a new level of continuous care and immediate contact between patients, care providers, and referral sub-specialists over secure web sites.

What separates CDMP from other applications in the marketplace?

- It leverages the expertise of leaders in diabetes management to oversee development of modules in three critical areas - in CDMP parlance, physical wellness, lifestyle modification and management, psycho-social health - and medical informatics.
- To respond to the diverse consortium populations, such an application must be a turtle - essentially, carrying its house on its back. CDMP's evolutionary path reveals a variety of embedded, portable features, developed in consensus - behavior assessment tool, risk-based care plan, basic online education catalog, knowledge assessment...

The story continues.

Continuous Non Invasive Venous Blood Glucose Monitor

Benny Pesach, Ron Nagar, Igor Belfer, Dalia Argaman, Shai Askenazi, Avner Adoram, Yossi Roffeh

Glucon Medical LTD. 70 Pinsker st. Petach-Tikva, 49130, Israel
Phone: 972-3-9347660 • Fax 972-3-9347662
benny@glucon.com

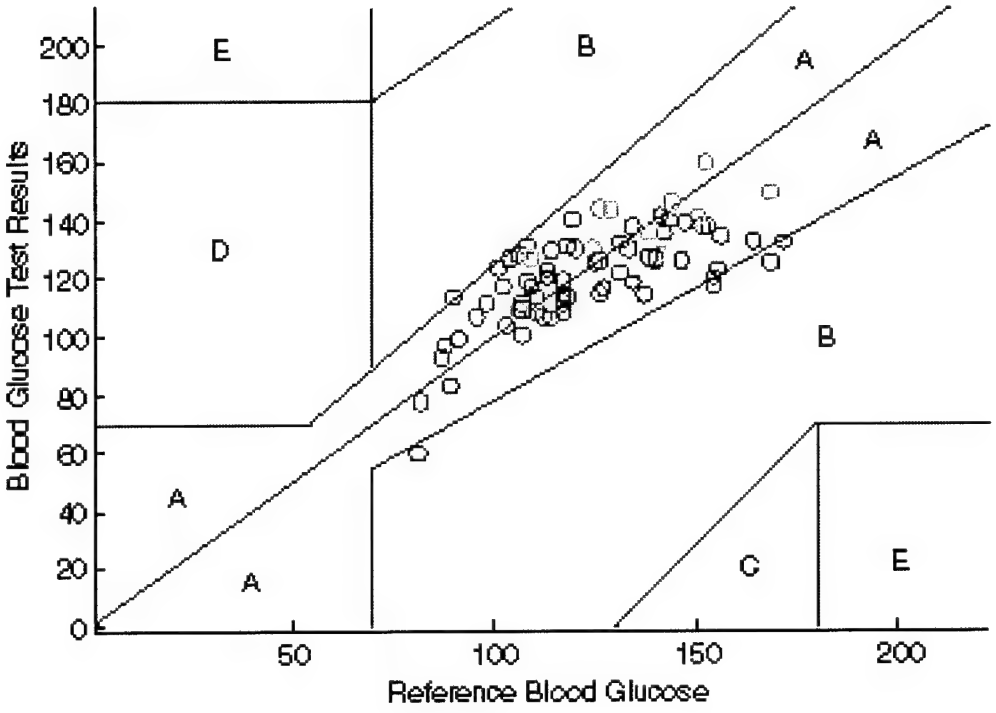
A new method for continuous Non-Invasive measurement of the Intra-Venous (IV) glucose level has been developed. The IV glucose level is the gold standard of the monitoring of glucose level for diabetic patients. It is the most accurate estimator for clinical decisions, especially for closing the loop with insulin pump in the future.

The measurement is based on the photoacoustic effect. The photoacoustic effect involves ultrasonic waves created by the absorption of light. These ultrasound waves are generated by illuminating the tissue with laser pulses at several selected wavelengths. Analysis of the acoustic signals can map the depth profile of the absorbance of light in the tissue. Anatomical structures and interfaces within the in-vivo tissue sample can be identified and analyzed independently of each other. Motion induced artifact can also be clearly identified and minimized. Optical wavelengths are selected to provide specificity to glucose and remove the influence of other substances present in the tissue sample.

Initial measurements on volunteer subjects were performed by a prototype device which was attached to the wrist. The measurements were preformed during 4 hours while systemic glucose levels were varied with a modified OGTT protocol. At least two high-low oscillations of the blood glucose level were captured for each subject. 45 data points were collected using finger stick from 7 subjects. The range of glucose levels for the entire population was 80 to 180. The typical precision was 13 mg/dl RMS and the pooled correlation coefficient for the population is 0.75.

This method provides an important step towards the implementation of a real-time fully non-invasive continuous blood glucose monitor.

The Clark Error Grid of the results (The reference is the Therasense FreeStyle finger stick):


Blood Glucose Test Results
Reference Blood Glucose
200
180
160
140
120
100
80
60
40
20
0
50
100
150
200
E
B
A
A
D
B
A
A
C
E

A Novel Selfcalibrating Method for Continuous Online Determination of Subcutaneous Tissue Glucose, Based on the Microdialysis Technique

Pfeiffer BM*, G Freckmann

*Institute for Diabetes-Technology
Helmholtzstr. 20, D- 89081 Ulm, Germany
Tel: +49 (0) 731 50 990 13 • Fax: +49 (0) 731 50 990 22
boris.pfeiffer@medizin.uni-ulm.de

Different attempts have been made to continuously monitor subcutaneous tissue glucose traces in man with some systems being in clinical use by now. However, most of these need to be calibrated retrospectively to blood glucose (BG) values.

By combining the 'recirculation-method' introduced by STERNBERG ET AL in 1995 [Diabetes Care, 18 (9): 1266-69] with a tubing-system allowing an automated two-point calibration during each cycle, we developed a system measuring the subcutaneous tissue glucose concentration (TG) in a 21 min interval without any further retrospective calibration steps to be done.

Using a Microdialysis catheter with a 30 mm membrane, a volume of 21 µL was recirculated in the system for 15 min, followed by a 6 min measuring period. In parallel, a two-point calibration was performed. The in vitro correlation between the measured glucose concentrations and reference in the range 2.2 - 17.0 mmol/L was very close. In 2 explorative experiments in fasting healthy non-diabetic volunteers, we found a BG of 3.7 +/- 0.3 (mean +/- SD) versus 3.7 +/- 0.4 mmol/L in TG and a BG of 3.2 +/- 0.2 versus a TG of 3.1 +/- 0.3, respectively. Performing a modified OGTT, the maximum BG-values were found to be 7.8 and 9.0 versus a maximum in TG of 4.7 and 7.5 mmol/L.

In order to get a better understanding of delays between blood- and tissue glucose traces, an absolute measuring device for tissue glucose is needed. The 21 min interval of this system is still to long to monitor rapid changes in glucose metabolism. However, this self-calibrating system allows absolute determination of subcutaneous tissue glucose concentrations and will make direct measurement of tissue glucose dynamics possible.

Increasing the Linearity of Enzyme-Based Amperometric Glucose Sensors by Adding Perfluorocarbon Emulsions to the Reaction

Pfeiffer BM[1], Freckmann G[1], Schosser A[1], Roehlke W[2], Franke RP[2], Haug C[1]

[1]Institute for Diabetes-Technology, University of Ulm, 89081 Ulm, Germany
Tel: +49 (0) 731 50 990 13 • Fax: +49 (0) 731 50 990 22
boris.pfeiffer@medizin.uni-ulm.de

[2]ZIBMT / Biomaterials, University of Ulm, 89081 Ulm, Germany

The range and linearity of oxidizing enzyme based biosensors such as glucoseoxidase-based enzymatic-amperometric glucose sensors for continuous monitoring is often limited due to a lack of oxygen for complete reaction. We therefore suggest to add a perfluorocarbon (PFC) emulsion to the reacting solution, as PFC´s are known to solve gases up to 20-fold better than water.
We prepared 4 different PFC-emulsions containing the enzyme glucoseoxidase and monitored the electrochemical signal of glucose solutions with known concentrations in a range from 30 - 330 mg/dL in vitro in a continuous flow mode using 3 different flow rates. As linearity in the range from 30 - 70 mg/dL is evident, the results were based on the linearity of this range and compared to the signals achieved, using PFC-free glucoseoxidase solution. A linearity factor (lf) was calculated according to the equation lf=((Sx-S30)/(cx-30)); Sx is the electrochemical signal of the glucose solution, S30 is the signal of a 30 mg/dL-solution and cx is the known concentration of the glucose solution. The deviation from linearity (DevLin) was calculated according to the equation DevLin (%) = [(lfx-lf70)/lf70]*100; lf70 is the linearity factor of a 70 mg/dL-solution.

The DevLin with PFC-free glucoseoxidase solution ranged from 37.7 +/- 20.3 % (mean +/- SD) to 31.3 +/- 17.6 %. Adding PFC-emulsion to the reaction decreased the DevLin, ranging from 10.6 +/- 6.5 % to 2.5 +/- 6.6 %, depending on the flow rate and the emulsions composition.

It has been shown, that adding a PFC-emulsion to the reaction of an enzymatic-amperometric glucose sensor increased the linearity of the sensor in the range from 30 - 330 mg/dL. The upper measuring range of such sensors, but also of other biosensors based on oxidizing enzymes, can be improved by adding PFC´s. A known problem of electrochemical sensors is the instability of the signal due to air bubbles in the flow system. According to our experiences, using PFC-emulsions minimizes this problem, as air bubbles do not appear in the system.

A Potentially Implantable Fluorescent Glucose Sensor based on Molecular Recognition in Poly(Ethylene Glycol) Hydrogels

Michael Pishko[1] and Gerard Coté[2]

[1]Department of Chemical Engineering and Department of Materials Science and Engineering, Pennsylvania State University, University Park, PA 16802
[2]Department of Biomedical Engineering, Texas A&M University, College Station, TX 77843

We have been pursing development of a fluorescence biosensor based on a photopolymerized poly(ethylene glycol) (PEG) hydrogel incorporating a fluorophore modified polysaccharide ligand (e.g. FITC-dextran) and a fluorophore modified glucose binding protein (e.g. TRITC-concanavalin A) chemically conjugated into the hydrogel network using an a -acryloyl, ω-N-hydroxysuccinimidyl ester of PEG-propionic acid. The focus of this work is the design and development of implantable, fluorescent-doped, intradermal polymer transducers that will be combined with an optical probe to quantify blood glucose levels. In this research, the fluorescence-tagged polymer microspheres will be injected below the skin. After implantation, the glucose specific fluorescently tagged polymer, when illuminated, will provide a noninvasive measurement of the fluorescence peaks that are proportional to the glucose concentration. In the absence of glucose, TRITC-Con A binds with FITC-dextran, and the FITC fluorescence is quenched through fluorescence resonance energy transfer (FRET). Competitive glucose binding to TRITC-Con A liberates FITC-dextran, resulting in increased FITC fluorescence proportional to the glucose concentration. PEG hydrogels were fabricated by photopolymerizing an aerosol sprayed from an ultrasound atomizer, producing microspheres from 1 to 1000 micrometers in diameters depending on the frequency and amplitude of ultrasound used. We will describe both in vitro experiments of hydrogel spheres suspended in a solution of phosphate buffered saline and glucose and in vivo experiments for spheres implanted subcutaneously in a hairless rate model.

Control and Automation for the Regulation of Blood Glucose in Type I Diabetic Patients via Parametric Programming

Efstratios N. Pistikopoulos[1]*, Pinky Panjwani[1], Vassilis Sakizlis[1], Vivek Dua[1], Francis J. Doyle III

1Department of Chemical Engineering, Centre for Process Systems Engineering
Imperial College, Prince Consort Road, London SW7 2BY, UK

2College of Engineering, University of California, Santa Barbara, CA 93106-5130

*Tel: +44-20-7594-6620 Fax: +44-20-7594-6606
e.pistikopoulos@ic.ac.uk

Automated control of the delivery of insulin to the diabetic patients is an important area of research. The use of control engineering tools for the delivery of insulin reduces the side-effects associated with the therapy and the human intervention and thus improves the living standard of the patient. The control engineering tools rely on developing a mathematical model of the patient, such as Bergman or Sorensen models, that can take into account the dynamic response of the patient to disturbances such as exercise and meal input while incorporating constraints on the blood glucose level of the patient and appropriate insulin delivery rate. This mathematical model is then used to predict the state of the patient at future times for the given state of the patient at current time and calculate the optimal amounts of the insulin delivery so as to minimize patient discomfort. Since the state of the patient keeps on changing with time, these calculations are repeated at regular time intervals. Due to the complex nature of the mathematical model, these calculations require the use of a computer. The objective of this work is to use advanced model based control algorithms for regulating the blood glucose in Type I diabetic patients without using an on-line computer. This is achieved by using novel parametric programming algorithm, developed at Imperial College, to obtain, off-line, the optimal insulin delivery rate as an explicit function of the current blood glucose level of the patient. The implementation of the optimal insulin delivery, therefore, requires simple function evaluation and minimal on-line computations. This is expected to greatly reduce patient inconvenience by a drug delivery mechanism, which is simple to realize and implement.

Detection of Glucose by Engineered Glucose/Galactose-Binding Protein and Surface Plasmon Resonance

J. Bruce Pitner, Helen V. Hsieh, Zachary A. Pfeiffer*, Terry J. Amiss, Douglas B. Sherman,

BD Technologies, 21 Davis Dr., Research Triangle Park, NC 27709-12016

*Department of Biomolecular Chemistry at the University of Wisconsin Medical School, Madison, WI 53706

Author	Tel	Fax	Email
Hsieh	919-597-6192	919-597-6400	Helen_V_Hsieh@bd.com
Pfeiffer	608-262-6206	608-262-5253	zapfeiffer@students.wisc.edu
Amiss	919-597-6125	919-597-6400	Terry_Amiss@bd.com
Sherman	919-597-6105	919-597-6400	Douglas_Sherman@bd.com
Pitner	919-597-6147	919-597-6400	Bruce_Pitner@bd.com

Monitoring and managing blood glucose levels is a key component for maintaining health of people with diabetes. Traditionally, glucose monitoring has been based on indirect detection using electrochemistry and enzymes such as glucose oxidase or glucose dehydrogenase. Here, we demonstrate direct detection of glucose using a surface plasmon resonance (SPR) biosensor. This was accomplished by site-specifically and covalently attaching a known receptor for glucose, the Glucose/Galactose-Binding Protein (GGBP) to the SPR surface. The site-specific coupling was accomplished by mutation of amino acids on GGBP to cysteine and subsequent thiol conjugation. The resulting SPR surfaces had glucose-specific binding properties consistent with known properties of GGBP. Further modifications were introduced to weaken GGBP binding affinity to more closely match physiologically relevant glucose concentrations (1-30 mM). A Kd of 0.5 mM was obtained with one triple mutant of GGBP.

Implementation of a New Insulin Model Covering both Injection and Pump Delivery in DiasNet

Søren Plougmann[1]*, Ole K. Hejlesen[1], David A. Cavan[2]

1Department of Health Science and Technology, Aalborg University, Denmark
2Bournemouth Diabetes and Endocrine Centre, Bournemouth, UK

*Department of Health Science and Technology, Aalborg University
Fredrik Bajersvej 7 D1, DK-9220 Aalborg, Denmark.
Phone +4596358782 Fax +4598154008
spp@hst.auc.dk

The core of DiasNet is a discrete difference compartment model of the human carbohydrate metabolism, consisting of two main compartments representing carbohydrate in the gut and glucose in the blood, on which processes representing various organ systems operate. Blood insulin is calculated from standard absorption profiles, which are modified by dose/peak relations for the specific specimen. This seems appropriate for insulin injections, but computing blood insulin levels from insulin continuously infused by a pump from this model is not appropriate due to the "single shot" nature of the current insulin model. A new prototype model for blood insulin levels has been implemented in DiasNet. It is a discrete difference compartment model, consisting of two main parts representing subcutaneous insulin and blood insulin. The subcutaneous absorption of insulin is influenced by an equilibrium model for the association state of insulin (low and high molecular weight, i.e. hexameric and dimeric) and subcutaneous diffusion, giving the desired characteristics of initial slow absorption (for soluble insulin) and volume and concentration dependencies. In the blood insulin compartment representing both the blood space and extravascular space, the absorbed insulin is degraded according to a first order process. The model is adapted to general blood insulin profiles for the different insulin types, whereas patient specific adaptation is handled through an insulin sensitivity parameter in DiasNet. Being integrated in the DiasNet decision support system the model is available to people with diabetes and healthcare professionals who are able to change insulin regimes and pump settings and immediately seeing the effect on the active blood insulin and blood glucose levels.

Application of Communication Technology to Allow Personalization of Diabetes Treatment Therapy to an Individual's Lifestyle and Treatment Needs

Rhall E. Pope, Michael Blomquist, Jay Johnson

Deltec, Inc.
1265 Grey Fox Road, St. Paul, MN 55112
sandy.dost@deltec.com

Type 1 diabetes is an extremely personal disease, both in its consequences if not treated properly and in the impact of treatment regimens on an individual's lifestyle. The Diabetes Control and Complication Trial (DCCT) concluded that the risk of serious complication from Type 1 diabetes can be greatly reduced through intensive insulin delivery therapy. This therapy typically takes the form of multiple daily injections (MDI) of insulin or continuous subcutaneous insulin infusion (CSII) with an insulin pump.

Insulin pumps, while providing effective intensive insulin therapy, have also provided greater flexibility in the delivery of the therapy and, for some individuals, reduced the impact of that therapy on their individual lifestyles. Communication technology, in the form of personal computers, laptops, handheld PDA's, and wireless communications have had even more dramatic impact on individual's lifestyles. This paper will describe how commercially available communication technology can be combined with insulin pump based diabetes treatment to allow individuals to aggressively manage their treatment regimen while easily and safely personalizing it to fit their lifestyle demands.

Fueling Your Diabetes Education Program Creative Approaches to Technology-based Marketing and Management

Beverly Price, RD, MA* and Donna Rice RN, BSN, CDE

*Jump Start Consulting, LLC
13123 Hart, Suite #1, Huntington Woods, Michigan 48070
Tel: 248-390-4150 Fax: 248-542-9938
BPLBS@aol.com
www.gettingthatjumpstart.com

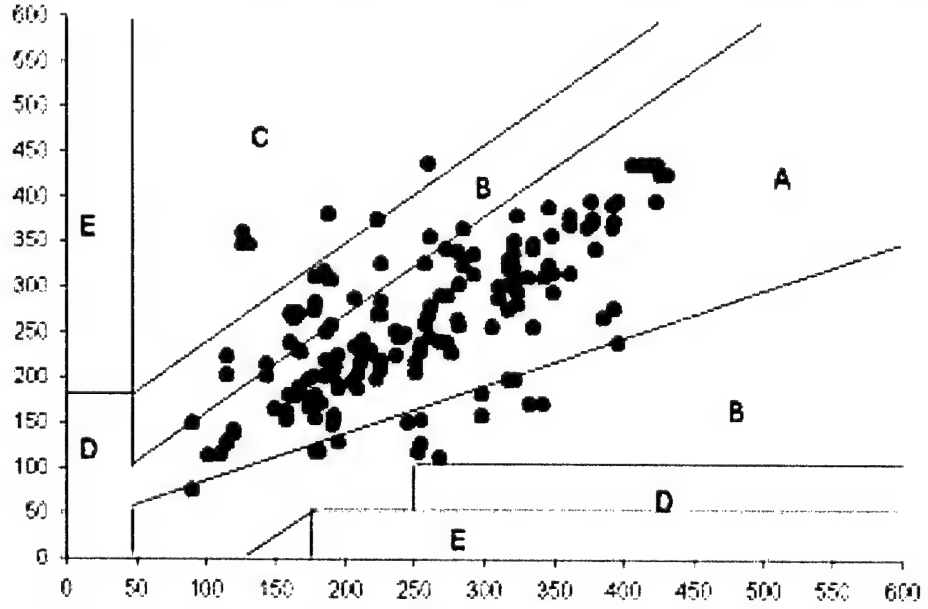
The "Information Age" has brought us an array of technology, including computerization. Studies show that the adult population is the fastest growing market segment using computers. In today's healthcare climate, effectiveness and efficiency are the keys to survival. Most ancillary departments tend to be hyper-focused on clinical skills but are unable to turn these skills into access, revenue and, in turn, measure revenue. As a result, diabetes self-management programs continue to face cutbacks, which therefore limits the available resources to the diabetes community. The purpose of this timely seminar is to bridge the gap between clinical and business knowledge of nursing and dietetics professionals, along with educating administrators, in order to be competitive in the current healthcare environment while filling the void in disease management. This interactive seminar will utilize the professional experiences of the presenters along with proven business techniques to teach participants how to maximize revenues for their department using marketing techniques such as fax blast, website development and bulk e-mail, along with development of presentation materials that educate and sell. Upon completion of the workshop, participants will be able to develop a technology-based marketing action and teaching plan for their diabetes education program. Participants will also be able to create a computer-based referral and revenue tracking system for their program.

Clinical Evaluation of a Micro-Invasive Glucose Detection System

Eric Raskas*†, Thomas Svetis*, Lingao Zhang*, Jamie Brauner*, Emma-Lee Taormina*, Valerie Rule*

(*all of MicroSense International, LLC, St. Louis, MO, †Presenter, eric.raskas@micro-sense.com, (314) 615-6969 (T), (314) 615-6324 (F), MicroSense International, LLC, 4041 Forest Park Avenue, St. Louis, MO 63108 USA, www.micro-sense.com

Adequate frequency of self-monitoring of glycemic levels via spot detection of capillary glucose in Type I & II diabetics have suffered from low patient compliance due to a variety of factors. Principal reasons cited by patients focus on the pain of self-testing and the blood required for measurements. A variety of alternative testing schemes have been proposed and developed to address these impediments to increasing the frequency of self-testing. Addressing the deficiencies in these approaches and overcoming the barriers to patient self-testing, MicroSense International, LLC (St. Louis, MO) has developed a painless, bloodless, micro-invasive single-use spot monitoring system consisting of a hand-held meter and single-use optical/enzymatic probe. Glucose concentrations are recorded within fifteen (15) seconds, following penetration of the optical/enzymatic probe 0.1mm through the outer dermis to the interstitial space. Glucose measurements are taken via glucose diffusion from the interstitial fluid to the surface of the optical/enzymatic probe, initiating a fluorescent indicator reaction, correlating to the patient glucose concentration. Phase I clinical evaluations the Pushita™ system in Type I & II diabetic patients have shown good correlation to commercially available glucose measurement systems. The clinical trial design consisted of glucose challenge tests ranging over four (4) hours with measurement taken every fifteen (15) and thirty (30) minutes. Modal representation of Pushita results vs. control measurements (both venous and capillary blood glucose levels taken simultaneously) demonstrated no lag in ISF glucose readings vs. control measurements. Clarke Error Grid analysis showed 97% correlation to Zones A & B. The authors will discuss the structure of Pushita™ and review the clinical experience to date.



Phase I Clinical Evaluation (22 patients) of Pushita™
Clarke Error Grid (97% Zone A&B)

Hybrid approach for insulin-dependent diabetes based on a telehealthcare decision support system

L. Roa, M. Prado, J. Reina-Tosina

Grupo de Ingenieria Biomedica, Escuela Superior de Ingenieria, University of Sevilla
Camino de los Descubrimientos, s/n, 41092 - Seville, Spain
Tel. 34 95 4487335 Fax. 34 95 4487340
laura@esi.us.es

A novel hybrid approach for the management of blood glucose level (BGL) in patients with insulin dependent diabetes mellitus (IDDM) is presented, based on a telehealthcare system. Taking into account the patient energy expenditure due to physical activity, this system will allow a more accurate control of BGL by a periodic insulin dose adjusted to the true patient metabolism.

Two key issues can be highlighted in the proposed system: the ability to monitor the patient energy expenditure in real time and the addition of a customized systemic dynamics model, which represents the glucose metabolism. This model defines a first signal-processing layer of the telehealthcare system, followed by a second layer based on more classical data-driven algorithms. This approach combines the higher predictive capability of physiological models with the demonstrated accuracy of current data-driven models to advise insulin dose when biomedical data are within previous trial range and have enough resolution.

The glucose metabolism mathematical model is integrated within a computational component, called patient physiological image (PPI), which represents a virtual image of the patient. This component can include other physiological models, which in turn may be coupled with the glucose model. This approach allows the assistance to multi-pathology chronic patients, as is the case of end state renal disease (ESRD) patients, whose first major diagnostic (ESRD incidence) is diabetes mellitus.
The energy expenditure is computed in real-time from the accelerations acquired with a novel portable device, currently patent pending. This device includes added values, as postural and kinematics supervision, which are very relevant for the adequate remote healthcare of chronic patients.

Using a Web-based Diabetes Risk Stratification Approach

James Rosenzweig, Sonya Celeste-Harris*, Katie Weinger, Diane Connor, Patricia Bonsignore, and James Garland

*Disease Management, Joslin Diabetes Center
One Joslin Place, Boston, MA 02219
Tel: 617 264-2770 • Fax: 617 732-2562
sonya.celeste-harris@joslin.harvard.edu

The increasing incidence of diabetes with its prevalence of complications and related high costs, and the existence of established clinical recommendations for the management of diabetes, call for the use of a comprehensive data management system that improves patient care and reduces variability in practice. Our web-based diabetes disease management tool assists health plans, providers, and case managers to organize and better manage the care of their patients. Following simple data entry, the system stratifies patients into risk categories and recommends targeted interventions to manage diabetes and cardiovascular, renal, retinal and peripheral vascular co-morbidities. Numerous links in the database lead users to screens showing clinical guidelines, defining risk level criteria, and identifying patients in each risk category. It has secure sockets, firewalls, backup/recovery, and ad hoc reporting capabilities. This system requires no software installation, only an Internet Explorer browser. Currently in the final phase of a three-year pilot project with four primary care practices, key process and outcome measures are being tracked. In an inner city community practice, mean A1C decreased from 8.8% to 8.2%, the percentage of patients with A1C <8.0% increased from 32 to 56, and percentage of patients with A1C <9.5% increased from 55 to 81. Documented foot examinations in the past year increased from 2% to 89%, urine albumin measurements increased from 7% to 42%. Frequency of lipid profile and blood pressure testing improved, and percentage of patients in target range increased. The provision of simple, focused reports fostered a cooperative approach to quality improvement. These findings suggest a bright future for web-based disease management tools.

Non-Invasive Measurement of HbA1c Using Near Infrared Spectroscopy

Samsoondar, James*; Kaushal, Ashwani; Lu, Geng; Lynch, Michael

*CME telemetrix Inc.
560 Parkside Drive, Waterloo, Ontario, Canada, N2L 5Z4
Tel: (519) 886 8440 Ex 229 Fax: (519) 886 8442
jsamsoondar@cmetele.com

Measurement of HbA1c in blood is essential in the clinical management of diabetic patients, used as an index of mean blood glucose concentration during the preceding 3 months. Near Infrared (NIR) spectroscopy was used to develop a rapid non-invasive method of measuring %HbA1c in blood. The non-invasive method involves collecting NIR radiation transmitted through a finger and developing a calibration algorithm using Partial Least Squares. The number of data points used for calibration was 492, collected from 56 different subjects-a mix of diabetic patients and non-diabetic persons. The accuracy and precision of the calibration algorithm was determined.

Accuracy

Over a period of 15 days following calibration, 132 data points were collected from 44 of the 56 patients. A linear regression plot with the predicted %HbA1c from the NIR test method on the y-axis and the %HbA1c from a reference method (DCA 2000 from Bayer), produced the following equation:
$y = 0.84x + 1.13$; $R2 = 0.76$. Ninety five percent of the results were within + 1% HbA1c. The error in the NIR method is overestimated due to error in the reference method, and a more accurate reference method for HbA1c would yield more accurate results for the NIR method.

Precision

Precision results are summarized in the table below:

Sample Description	Sample Size (time span)	Standard Deviation	Mean	% Coefficient of Variation (CV)
Non-diabetic person	40 (6 days)	0.23	5.6	4.1
Artificial Finger*	23 (23 days)	0.27	11.2	2.4

*A custom-made Quality Control Tool

The results shown above are within the certification criteria of the National Glycohemoglobin Standardization Program. Studies using a larger patient population and a more accurate reference method for HbA1c are underway.

Regulatory Considerations for Invasive and Non-Invasive Glucose Measurement Devices

Harry Sauberman, MEE, PE

hrs@cdrh.fda.gov

Manufacturer submissions to the FDA for invasive glucose measurement devices are generally 510(k) premarket notification applications. In this process, a manufacturer is asked to show that their device is "substantially equivalent" to a predicate device that has been legally approved for marketing. The concept of "substantial equivalence" will be discussed in terms of the type of information needed to support an SE determination. Non-invasive glucose measuring devices, on the other hand, are considered to be high risk medical devices that require premarket approval (PMA) with data from both laboratory and clinical studies to substantiate the claims for intended use. The PMA process will be discussed as it is applicable to these devices.

Control of Blood Glucose in Patients with Type 1 DM with the MPC Algorithm under Daily Life Conditions

HC Schaller[1,2]*, L Schaupp[1,3], M Bodenlenz[1,2], A Wutte[1], J Plank[1], R Sommer[1], H Zapotoczky[1], B Semlitsch[1], LJ Chassin[4], ME Wilinska[4], R Hovorka[4], T Vering[5], P Wach[2], TR Pieber[1]

[1]University Graz, Austria
[2]Graz University of Technology, Austria
[3]Joanneum Research, Graz, Austria
[4]City University London, UK
[5]Disetronic Medical Systems AG, Switzerland

*Department of Biophysics, Institute of Biomedical Engineering, Graz University of Technology
Krenngasse 37, 8010 Graz, Austria
Tel: 0043(0)316 873 5339 Fax: 0043(0)316 873 5340
schaller@microperfusion.at

Aim: The aim of this study was to evaluate the ability of the Model Predictive Control (MPC) algorithm to control blood glucose (BG) in patients with type 1 DM under daily life conditions using simulated subcutaneous glucose measurements (SGM) and continuous subcutaneous insulin infusion (CSII) (simulated SC-SC route).

Methods: 11 patients on CSII therapy came to the clinic at 2p.m.. In a 3.5hour period their BG concentration was clamped to 6mmol/l. At 6p.m. they had dinner. The prandial insulin doses were determined according to individual needs. At 7:30p.m. the MPC algorithm took control over the CSII for 26.5hours. Calculation of insulin infusion rates was based on intravenous glucose values delayed for 30minutes so as to simulate the maximum delay time of SGM. The next day patients had breakfast (7a.m.), lunch (12a.m.) and dinner (6p.m.). The boluses for these meals were calculated by the MPC taking into account the amount of carbohydrate intake.

Results: One single hypoglycaemic event (BG<3.3mmol/l) occurred due to insulin infusion by the MPC.

		BG(Mean±SD) [mmol/l]
10p.m. first day		6.9±2.4
2a.m. next day		7.0±1.2
Before	breakfast	6.0±0.8
2hours after	breakfast	10.2±1.9
Before	lunch	5.7±1.5
2hours after	lunch	8.5±1.9
Before	dinner	6.3±1.1
2hours after	dinner	9.0±1.4
10p.m. next day		6.5±1.3

Conclusion: BG in patients with type 1 DM can be controlled with the MPC in a simulated SC-SC route under daily life conditions.

Use of a Noninvasive Elasticity Measurement to Determine Response to Amadorase Inhibition in a Diabetic Rat Model

Michael L Schwartz, Ph.D.

Dynamis Therapeutics, Inc.
805 E. Willow Grove Ave, Suite 2C, Wyndmoor, PA 19038
Tel: (215) 402-9347 Fax: (215) 402-9345
MLSchwartz@Dynamis-Therapeutics.com

Dynamis Therapeutics, Inc. has performed an experiment designed to look at the effect of 3-deoxyglucosone (3DG) reduction on skin elasticity in STZ-diabetic and non-diabetic rats. Skin elasticity was measured using a non-invasive device (DermaLab®; CyberDERM) that works by determining the amount of vaccuum pressure required to displace skin past a probe located inside a suction cup probe that is adhered to the skin. The more pressure that is required to displace the skin, the less elastic the skin. 9 STZ-diabetic and 6 non-diabetic rats were given daily subcutaneous injections of Dynamis' proprietary small molecule drug, DYN 12, at a concentration of 50 mg/kg. Dynamis has previously demonstrated that DYN 12 reduces systemic 3DG levels in diabetic and non-diabetic rats by approximately 50% by inhibiting the enzyme Amadorase. Amadorase is a fructosamine-3-kinase that is reposnsible for the enzymatic production of 3DG. 10 STZ-diabetic and 6 non-diabetic rats were injected with saline as controls. The amount of pressure needed to displace the skin of diabetic rats on saline was approximately 2.25-fold higher than that of diabetic rats on DYN 12 (7.2±3.0 vs. 3.2±1.2, $p = 0.001$). The elasticity value observed with diabetic rats on DYN 12 was not statistically different from the value from non-diabetic rats on saline ($p = 0.26$) or non-diabetic rats on DYN 12 ($p = 0.39$). These data demonstrate that the administration of DYN 12 to diabetic rats prevents the loss of skin elasticity observed in untreated diabetic rat and that reducing systemic 3DG prevents the stiffening of skin associated with diabetes.

Reverse Iontophoresis for Non-Invasive and Calibration-Free Glucose Monitoring *In Vivo*

A.Sieg, R.H. Guy, M.B. Delgado-Charro

School of Pharmacy, University of Geneva
Centre interuniversitaire de recherche et d'enseignement
Campus universitaire, Parc d'affaires international
F-74166 Archamps
Phone: +33 (0)4 50 31 55 30 • Fax: +33 (0)4 50 95 28 32
Anke.Sieg@pharm.unige.ch

The GlucoWatch® biographer (Cygnus, Inc.) uses reverse iontophoresis to noninvasively extract glucose across the skin, allowing glucose levels to be followed over 12 hours. However, the device must be calibrated with a blood sample assayed in the conventional way. Our objective is to avoid this invasive step.

Reverse iontophoresis was performed in vivo on six healthy volunteers. The Ag/AgCl electrode compartments were small glass cells fixed to the ventral forearm. The anode chamber was filled with Tris-buffered normal saline; the cathode chamber contained Tris buffer alone. Constant current was passed for five hours and the cathodal solution was withdrawn and analysed every 15 minutes for the quantities of Na+ and glucose extracted by "reverse" electromigration and electroosmosis, respectively. Two hours after starting the experiment, blood glucose levels were measured with a traditional glucose monitor at the beginning and end of the iontophoretic interval.

While the extracted Na+ flux was invariant, as expected given the essentially fixed NaCl concentration present in the physiological system, the glucose samples reflected proportionately the subdermal concentration. Equally, the extracted flux ratio (glucose/sodium) varied linearly with the subdermal glucose/sodium concentration ratio; knowing the gradient of this correlation, therefore, means that a measurement of the extraction flux ratio can be used to determine the subdermal glucose concentration (the physiological [Na+] being known and fixed).

Thus, a refinement of the reverse iontophoresis technology using the simultaneous determination of the extracted fluxes of the analyte of interest (glucose) and of an "internal standard", whose level in the biological system is invariant (Na+), may permit a noninvasive sampling methodology free of the need for calibration with a blood sample.

This work was supported by the Programme commun de recherche en génie biomédical, Switzerland.

Bolus Insulin Delivery Through Micropores in Skin via Electrotransport in Human Subjects

Alan Smith*, Ph.D., Teresa Woods, B.S., Deidre Williams, B.S., Harry Delcher, M.D., Jonathan Eppstein, M.S., Morgan McRae, M.S., Michael Hatch, M.S.

*Altea Development Corp.
2056 Weems Road, Atlanta, GA 30084-5207
Tel: (770) 270-0398 Fax: (770) 270-0399
asmith@alteatech.com
http://www.alteatech.com

Historically, transdermal delivery of insulin has been limited by the barrier function presented by the outermost layer of skin, the stratum corneum. A pharmacokinetic study of lispro insulin delivered using microporation and electrotransport was performed on 12 non-diabetic volunteers. A rectangular array of shallow, microscopic pores was created through the stratum corneum of the volar forearm by contacting a set of small, rapidly heated elements to the skin surface. An iontophoretic patch (TransQ2, Iomed) containing a silver-silver chloride electrode and hydrogel sponge was filled with insulin lispro (Humalog U-100, Eli Lilly) and applied over the array of micropores. A counter electrode composed of gum karaya (Iomed) was placed adjacent to the delivery electrode. Cathodic electrotransport was implemented with a 50% duty cycle (2.5 min on, 2.5 min off) and an average current of 1 mA. After 75 minutes of modulated electrotransport, the patch was removed. Serum samples and fingerstick blood glucose measurements were taken every 15 minutes for 3 hours. Mean serum lispro levels reached a peak of 12 mU/mL at the end of the delivery period and dropped immediately back to baseline after the patch was removed. A pharmacodynamic study (euglycemic clamp) on 11 subjects confirmed that insulin delivered through micropores under electric current was bioactive and showed a significant peripheral tissue response based on the glucose infusion curves. This initial work is encouraging and may lead to the development of a needle-free painless patch technology to achieve basal and bolus insulin delivery profiles in people with diabetes.

Basal Insulin Delivery Through Micropores in Skin in Human Subjects

Alan Smith*, Ph.D., Teresa Woods, B.S., Deidre Williams, B.S., Harry Delcher, M.D., Jonathan Eppstein, M.S., Morgan McRae, M.S.

*Altea Development Corp.
2056 Weems Road
Atlanta, GA 30084-5207
Tel: (770) 270-0398 Fax: (770) 270-0399
asmith@alteatech.com

Altea has developed a noninjectable insulin infusion system that utilizes patch technology for the basal delivery of insulin through the skin. This patented patch technology is able to overcome the skin's natural barrier to the absorption of large molecular weight proteins and peptides. Painless transdermal insulin infusion provided by this patch is demonstrated as an alternative to continuous subcutaneous insulin infusion by an insulin pump (CSII) or to intermediate and long-acting injectables. A pharmacokinetic study was performed in 20 non-diabetic volunteers to evaluate this system with a commercially available insulin lispro formulation in a liquid reservoir patch. Shallow microscopic pores were created through the stratum corneum of the volar forearm in a rectangular array by a painless thermal microporation process. A liquid reservoir patch was filled with U-100 insulin lispro (Humalog®, Lilly) and applied over the array of micropores for 6 or 12 hours. Serum samples were taken every hour and analyzed for lispro insulin content with a radioimmunoassay specific for lispro insulin. Both the 6-hour and 12-hour patch demonstrated steady lispro infusion with a serum Cmax of 13 μU/ml at a Tmax of 6 hours. On average, serum insulin lispro levels were maintained above 5 μU/ml from 1 hour after patch application until patch removal at 6 or 12 hours. After patch removal, serum levels declined back to baseline in approximately 2 hours. Transdermal basal insulin infusion has been achieved using an approved insulin formulation without the use of chemical enhancers, iontophoresis or ultrasound. Longer-term studies are underway to develop a convenient 24-hour insulin patch to provide painless, needle-free, basal insulin delivery for people with diabetes.

Engineering Enzymes for Continuous Glucose Monitoring System

Koji Sode

Department of Biotechnology, Tokyo University of Agriculture & Technology
2-24-16 Nakacho, Koganei, Tokyo 184-8588 Japan
Tel/Fax; Int-81-42-388-7027
sode@cc.tuat.ac.jp

The most popular enzyme for self blood glucose monitoring is glucose oxidase (GOD) due to its durable enzymatic characteristics together with the availability on the market. The current major increasing products in self blood glucose monitoring are the electrochemical enzyme sensors that are based on the electrochemical measurement of reduced artificial electron mediator resulting from the enzymatic oxidation of glucose. Considering the inherent problem of GOD that it utilizes oxygen as the electron acceptor, pyrroloquinoline quinone glucose dehydrogenase (PQQGDH) is being considered as the ideal enzyme for electrochemical sensors due to its oxygen insensitive property and excellent catalytic efficiency. The authors have been engaging in the engineering of PQQGDHs to achieve the construction of the most ideal enzyme for glucose enzyme sensors. We have already reported protein engineering of PQQGDHs, and succeeded in the construction of engineered enzymes with increased catalytic efficiency, substrate specificity, stability, bio-processes for the recombinant PQQGDH production, and also enzyme sensor employing engineered PQQGDHs.

The recent trend in enzyme glucose sensors in blood glucose monitoring is the development of Continuous Glucose Monitoring Systems (CGMSs). The criteria and requirements for enzyme and chemistry to be utilized in CGMS are different from those in disposable enzyme glucose sensors. CGMSs so far reported utilize GOD as the enzyme and the detection is based on the hydrogen peroxide electrochemistry. Here I report our challenges in the development in the CGMS employing engineered PQQGDHs. We constructed CGMS using engineered PQQGDH with increased lifetime suitable in the application for continuous operation. The future prospect of CGMS employing PQQGDHs together with the available electrochemical principles are also being discussed.

Non-Invasive Monitoring of a Bioartificial Pancreas

Cherie L Stabler[1], Robert C. Long, Jr.[2], Ioannis Constantinidis[3], and Athanassios Sambanis[4]

[1]Corresponding author/presentor
Department of Biomedical Engineering, Georgia Institute of Technology/Emory University,
315 Ferst Drive, Atlanta, GA 30033,
Tel: (404)727-9838 Fax: (404)727-5869
gte445k@prism.gatech.edu

[2]Fredrick Philips Magnetic Resonance Research Center
1364 Clifton Road, Atlanta, GA 30322
Tel: (404)727-4570 Fax: (404)727-5869
rlong@emory.edu

[3]Division of Endocrinology, Department of Medicine, University of Florida,
1600 SW Archer Road, Gainesville, FL 32610,
Tel: (352)846-2227 Fax: (352)846-2231
consti@medicine.ufl.edu.

[4]Department of Biomedical Engineering, Georgia Institute of Technology/Emory University
315 Ferst Drive, Atlanta, GA 30033
Tel: (404) 894-2869 Fax: (404) 894-2291
athanassios.sambanis@che.gatech.edu.

Within the field of tissue engineering, there is a great need to develop methods to monitor the function and morphology of an implant in vivo. Non-invasive monitoring using Nuclear Magnetic Resonance (NMR) imaging and spectroscopy can prove to be the solution to this problem by providing detailed information concerning the structure of the construct and the metabolic activity of the implanted cells. Water suppressed 1H NMR spectroscopy has the ability to assess cellular construct viability by providing valuable information about the levels of important metabolic markers, such as choline, while 1H NMR imaging allows for high resolution imaging of the implanted construct. In this study, we have applied these NMR methods to monitor ?TC3 cells contained within planar constructs as a model bioartificial pancreas for the long-term treatment of diabetes. Preliminary in vivo 1H NMR studies on C57-BL/6J mice have established that accurate spectroscopic data and informative images can be collected from a construct of 0.3mL in volume within a total time frame of only 30 minutes. Current work is focused on refining our implantable construct to be functional, retrievable and appropriate for NMR imaging and spectroscopic studies. This construct, in turn, is used within streptozotocin-induced diabetic mice and its functionality is assessed by correlating 1H NMR imaging and spectroscopy data to the blood glucose levels of the animal. Implications of this research include the ability to non-invasively obtain metabolic and morphological information on implanted tissue substitutes.

Closed-Loop Physiologic Insulin Delivery: How to Choose Controller Gains

Garry M. Steil, Mikhail Loutseiko, Natalie Kurtz, Antonios Panteleon, Kenny Long, Jake Leach, and Kerstin Rebrin[1]

[1]Director Closed-Loop Program
Medtronic MiniMed
18000 Devonshire Str., Northridge, CA 91325
Tel: (818) 576 4156 • Fax: (818) 576 6206
kerstinr@minimed.com

Closed loop insulin delivery has the potential to dramatically improve glucose control. Ideally, a closed-loop system would emulate plasma glucose and insulin profiles seen in an individual with normal glucose tolerance (NGT). In NGT individuals, the ß-cell responds to glucose challenges with a biphasic (first and second phase) response with the magnitude tightly linked to the individual's insulin sensitivity (first phase insulin times insulin sensitivity = constant). In the present study, an external physiologic insulin delivery (ePID) system capable of reproducing the biphasic insulin response was evaluated in 4 diabetic dogs. The ePID system is comprised of a subcutaneous (sc) glucose sensor and an external insulin infusion pump (MiniMed 508) telemetrically linked to a computer. The ratio of first to second phase insulin delivery was chosen to compensate for the delay in sc insulin absorption, and the magnitude of the controller response was adjusted according to the dog's insulin sensitivity (estimated from the dog's daily insulin requirement). To test the robustness of the system to day-to-day changes in insulin requirement (i.e., changes in insulin sensitivity and/or clearance) additional closed-loop meal responses were obtained under condition where the closed-loop gain was reduced and increased by 50%. In all cases, stable fasting glucose was obtained within the target range (80-120 mg/dl). Meal area-under-curve (AUC) decreased with increasing gain. At the highest gain (1.5 times DIR), the meal; response had a tendency to oscillate indicating any further increase in gain could potentially result in excessive swings in glucose. We conclude that, in dogs, the ePID algorithm can be tuned using a single parameter (DIR) and that the resulting control will be robust to approximately 50% changes in closed-loop gain.

Alginate Encapsulation - What Went Wrong

Rick Storrs, Ph.D.

2180 Palou Ave., San Francisco, CA 94124
Tel: (415) 643-2763 • Fax: (415) 643-2764
Rick@hanumanmedical.com

Alginates have an extensive but disappointing history in cellular encapsulation. Promising preliminary results, usually in rodents, cannot be repeated or fail in longer-term study. These results are due in part to use of uncharacterized alginate preparations that are impure or of too low molecular weight. Recently the ASTM has published standards for characterization and testing of alginates for biomedical and tissue engineering applications including determination of the average molecular weight, saccharide composition and sequence as well as the purity with respect to contamination by proteins, fucans and endotoxin. However even with the appropriate material these devices can fail because of a deleterious host response. This can take two forms, immunological sensitization due to incomplete coverage and foreign body encapsulation or fibrosis. In addition to innocuous surface chemistry, avoidance of fibrotic host response is dependent on a smooth surface texture. It is important to distinguish these failure modes of a cellular encapsulation device. Choices of material composition, molecular weight, purity and gelling cation, as well as device dimensions, surface texture and continuity will ultimately determine the success of the implant.

Toward the Development of a Pancreatic Tissue Substitute: Preproinsulin mRNA Engineering and its Application to the Regulation of Insulin Secretion from Human Hepatomas

Shiue-Cheng Tang (presenter) and Athanassios Sambanis (corresponding author)

Georgia Tech-Emory Center for the Engineering of Living Tissues
P.H. Petit Institute for Bioengineering and Bioscience, and School of Chemical Engineering
Georgia Institute of Technology, Atlanta GA 30332
Fax: 404-894-2291
gte343k@prism.gatech.edu
athanassios.sambanis@che.gatech.edu

Genetic engineering of non-ß pancreatic cells for glucose-responsive insulin secretion offers significant promise in developing a cell-based therapy for insulin-dependent diabetes. These cells are potentially autologous, retrieved as a biopsy from the patient, and thus relax the immune acceptance problems existing with allo- and xenogeneic cells. Responsiveness to physiologic stimuli is introduced at the gene transcription level by using promoters up-regulated by glucose and possibly down-regulated by insulin. A problem with these cells is the sluggishness in their secretion dynamics, which makes them inappropriate for glycemic regulation in higher animals and, eventually, humans. Of particular significance is the sluggishness of down-regulation of secretion, which results in the cells secreting insulin long after the stimulus has been removed, and may thus revert diabetes to hyperinsulinemia and hypoglycemia, a serious pathological condition.

We are investigating methods to improve the dynamics of down-regulation of insulin secretion. One method involves innovative engineering of the preproinsulin (PPI) mRNA through application of nonsense-mediated mRNA decay (NMD). The engineered PPI mRNA contains three consecutive copies of insulin gene with stop codons in the middle of the transcript to induce NMD. When the engineered PPI mRNA was expressed, a faster decline of PPI mRNA level and of insulin secretion rate was achieved upon switching off transcription, compared to the one-copy non-engineered control. This work provides a simple and straightforward method to decrease the stability of mRNA, specifically of the preproinsulin mRNA. The results are expected to be generic in nature, enabling expedited dynamics of secretion down-regulation in different host cells expressing recombinant proteins under transcriptional control. These findings have important ramifications in regulating gene expression in transcriptionally controlled cells, which are becoming increasingly important in tissue engineering and gene therapy approaches for treating insulin-dependent diabetes and other metabolic diseases.

Development of a New Device for Closed Type Self-monitoring Blood Glucose with Automatic Blood Sampling, Measuring, and Talking System for Blind Diabetic Patients

K. Tanzawa[1]*, Y. Uchigata**, M. Nishikawa**, Y. Iwamoto**

* Diabetes Business, Home Healthcare Company, Terumo Corporation, Tokyo
** Diabetes Center, Tokyo Women's Medical University School of Medicine, Tokyo,
***Konan branch, National Behcet Association, Saitama. Japan

[1]Diabetes Business, Home Healthcare Company, Terumo Corporation, Tokyo
2-44-1, Hatagaya, Shibuyaku-ku, Tokyo, 151-0072 Japan
kazuhiko_tanzawa@terumo.co.jp
Tel: +81-3-3374-8186 Fax: +81-3-3374-8273

It is difficult for blind diabetic patients to measure blood glucose by themselves. Moreover, it is quite difficult for them to put the tiny fingerstick blood to the teststrip belonged to any device. A new device has been developed, which is the closed type self-monitoring blood glucose device with automatic blood sampling, measuring, and talking system (Medisafe EZ Voice, Terumo Corporation, Tokyo). We investigated advantage and disadvantage of the device according to questionnaire for the blind diabetic patients.

Patients: 3 blind patients with type 1 diabetes and 3 with type 2 diabetes (male 2, female 4, age 20-50).

Materials: Medisafe EZ Voice by the glucose oxidase method has the test-strip attached to lancet en bloc, in which the process from blood sampling (4ul) to expression of blood glucose level by Japanese is automatically done. [Method] The evaluation of the device by questionnaire was done.

Result: All of the patients had accomplished measuring their blood glucose by themselves. The convenience to set up the device was achieved by the integrated tip. All of them were able to measure fingerstick blood glucose by themselves because auto-collecting blood from their fingers and auto-applying the blood to the test strip. Moreover, they were able to do the procedure well by the sound guidance and get the blood glucose level in Japanese after measurement.

Conclusion: We developed a self-monitoring blood glucose device for the blind patients which is done automatically from blood sampling to obtain the blood glucose level in Japanaese.

In vivo Evaluation of Engineered Insulin-Producing-Cells after Microencapsulation and Transplantation into Diabetic Mice

Pnina Vardi, Marina Vorobeychik, Karina Yavrians, Dmitry Azarov, Konstantin Bloch

Laboratory for Diabetes and Obesity Research, FMRC, Sackler Faculty of Medicine
Tel-Aviv University
Petah Tikva, Israel
Tel: + 972 39376280 Fax: +972 39211478
pvardi@post.tau.ac.il

Insulin producing beta-cell lines constitute a potential source to replace the difficult-to-obtain human pancreatic islets for transplantation. Most data reporting on the engineered characteristics of such cells were obtained during in vitro culture, but little was confirmed after transplantation. The aim of our study was to evaluate the functional activity and morphology of engineered insulin-producing-cells after microencapsulation and transplantation into diabetic mice. Parental low differentiated RINm, and streptozotocin (STZ) selected RINmS cells with improved functional activity were microencapsulated in alginate/PLL, and transplanted into the peritoneum of STZ-induced diabetic mice. The insulin content and response of the encapsulated cells to various secretogogues were studied before and three weeks after transplantation. The cell morphology was determined by histological analysis, while immunohistochemistry was used to evaluate the intensity of the insulin and samatostatin staining. Encapsulated cells cultured in vitro for a period of three weeks were used as a control group. We found that upon encapsulation and transplantation, selected RINmS cells did not lose their in-vitro acquired characteristics, as reflected by significantly higher insulin content and response (immunohistochemistry & RIA) to a mixture of glucose with IBMX or KCl, when compared to parental cells, both in vitro or in vivo. Our results show that at least during the first post transplantation weeks, the improved characteristics of engineered RINmS cells were maintained in vivo.

Needle-Free Insulin Administration Significantly Alters Nocturnal Blood Glucose Profile with Intermediate-acting Insulin in Type 1 Diabetic Subjects

M. Velussi

Diabetic Clinic "Pineta del Carso"
Via IX Giugno 21, Monfalcone, Italy
Phone: 40-3784177 • Fax: 48-1412005
Mario.velussi@libero.it

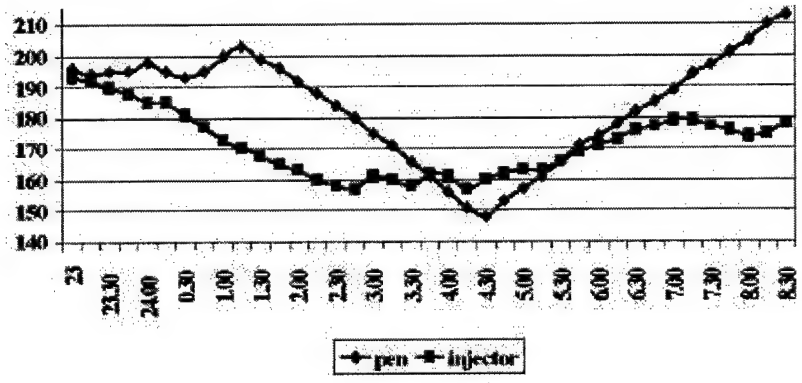
Introduction: The management of nocturnal NPH insulin is commonly a problem for type 1 diabetic patients because of hypoglycemia risk. Aim of the study: To compare nocturnal blood glucose after NPH insulin administered alternatively with a pen-like needle device and a needle-free jet-injector (Medi-Jector VisionÒ).

Materials and Methods: 15 type 1 diabetic subjects (7 males, 8 females), age 31+4 and diabetes duration 9+4 years, BMI 23,5+1,8 Kg/m2, systolic BP 130+4 and diastolic BP 78+4 mmHg, intensively treated since diabetes onset (43+5 I.U. insulin with NPH typically 30% of the total dose). Subjects consented to 72 hours continuous subcutaneous glucose monitoring (CGMS MinimedÒ) while using the pen device the first and the third night and jet-injector the second night of the study. Subjects received NPH at 11.00 pm. each night. All the patients otherwise maintained consistent activity, insulin dose and diet during the study.

Results: Blood glucose after using the jet-injector was significantly lower than that with a pen device between 12:30 AM to 3:30 AM and between 5:30 AM and 8:30 AM ($p<.01$) (see graph). The pen device produced somewhat lower blood glucose levels between 4:00 AM and 5:00 AM. No hypoglycemic episodes were recorded during the study.

Conclusions: The night-time blood glucose profile was improved using the jet-injector compared to a pen device. Blood glucose control with jet injection was superior at the end of the dosing period, and the blood glucose nadir was less pronounced after jet-injection. The needle-free injector may reduce the risk of nocturnal hypoglycemia in type 1 patients injecting bedtime NPH insulin.

Night-Time Glycemic Profile With NPH After Pen Device and Jet-Injector



One-year Pilot Study with a Needle-free Insulin Jet-injector Supports Sustained Improvement in Hba1c and Blood Sugar Profiles in Type 1 Diabetic Subjects

M. Velussi

Diabetic Clinic "Pineta del Carso"
Via IX Giugno 21, Monfalcone, Italy
Phone: 40-3784177 • Fax: 48-1412005
Mario.velussi@libero.it

Introduction: In a short-term study of a needle-free insulin jet-injector, the Medi-Jector VisionÒ, blood glucose profiles improved compared to that for pen devices in type 1 diabetic subjects. If sustained over time, this finding should result in improved HbA1c levels.

Aim of the study: To document HbA1c levels in subjects using the jet-injector and to measure their blood glucose profile after one year.

Materials and Methods: Five type 1 diabetic patients (3 females, 2 males) had the following profile: age 34+4 years, diabetes duration 9,5+4,5 years, BMI 23+1,2 Kg/m2, systolic BP 126+6 and diastolic BP 76+3 mmHg, daily insulin dose 36+4 IU/day (70% Regular, 30% NPH). All subjects consented to periodic HbA1c evaluations and 72-hours continuous subcutaneous glucose monitoring. A baseline glucose profile was obtained while subjects used a pen-like needle device. Subjects were switched to a jet-injector for one year, and a blood glucose profile was then obtained at one year. The monitoring periods were performed during working days, with the consumption of a stable diet (breakfast 430+30, meal 860+55, supper 660+45 Kcal) with 56% carbohydrates, 19% proteins, 25% fats) and minimal physical activity. Regular insulin was injected 30 minutes before food consumption, and NPH was injected at bedtime.

Results: HbA1c level decreased from 7,3+0,4% at baseline to 6,7+0,4% after six month and 6,3+0,2% after one year. Daily glucose profiles observed at the end of one year of jet-injection consistently showed lower postprandial blood glucose compared to the baseline (see graph).

Conclusion: Subjects experienced a continuous decline in HbA1c over one year of jet-injection insulin therapy. Improvements in the blood glucose profile using a jet-injector could be demonstrated with continuous monitoring.

A Wireless Diabetes Management and Communication System

Robert A. Vigersky[1], Eric Hanson, Edward McDonough, Timothy Rapp, and Robert S. Galen

[1]Corresponding/Presenting Author.
Diabetes Institute, Walter Reed Health Care System
6900 Georgia Ave., N.W., Washington, D.C. 20307
Telephone - 202-782-6750 • Fax - 202-782-0187
robert.vigersky@na.amedd.army.mil

Current intensive management of diabetes mellitus relies heavily on the patient to collect, tabulate, and communicate a large body of complex information (e.g. blood sugars, insulin dose, meal content, and exercise). This information is generally given to his/her provider manually at the time of the clinic visit. Affording patients the ability to amass and deliver these data conveniently and wirelessly and allowing the provider to respond in "real time" would overcome two major impediments to achieving improved glycemic control and reducing complications - forgotten/ incomplete information brought to the clinic and infrequent inter-visit communication. It recently became possible for a blood glucose meter to communicate with a personal digital assistant (PDA) via infrared windows. By using commercially available and custom software imbedded in the PDA, the combined device will be capable of noting relevant events (exercise, meals, basal, bolus, hypoglycemia, ketoacidosis, etc), prescription drug usage, and carbohydrate intake in addition to blood sugar information. This creates the first comprehensive portable, wireless diabetes management and communication system (DMCS). The data from the PDA will be wirelessly transmitted to the HealthSentry website (www.healthsentry.net) where data will be automatically analyzed and displayed in both numeric and graphic format. The data remains on the HealthSentry server to allow for historical trends to be clinically evaluated. we will take advantage of the currently utilized HealthSentry web-based glucose evaluation program for data collection and analysis. We will assess impact of this DMCS on glycemic control (as determined by hemoglobin A1c levels) in 20 highly motivated patients, i.e. insulin pumps users in a randomized, crossover study and analyze the information assurance and HIPAA implications of PDA use and wireless data transmission.

Diatech Control Project: A Systemic Integration of Diabetes Care

Marcia Walker-Guy, R.Ph, M.E.D, Pharm. Dc*, David Bourne, Ph.D.

*8201 Peters Rd, Suite 1000, Plantation, FL 33324
Tel: 954.916.2733 Fax: 954.916.2729 & 954.583.2353
marcia@infomedpa.com
http://www.infomedpa.com

Purpose/Background:
The need for an effective chronic care delivery system has had significance impact on US healthcare dollars. Keeping up with expanding patient load and therapeutic application of knowledge is critical. Adhering to the American Diabetes Association (ADA) Standards of care will ensure the quality and consistency in care. For practitioners to function effectively, the system must support adjustment of patient specific therapy, and acquisition and application of evidence to a specific clinical situation.

Methodology
This randomized control study design seeks to evaluate telemedicine's effect on improving clinical care outcomes through the information management of evidence-based diabetes. This initial small group study includes 60 patients; ages 65 and older with a team of diabetes care providers supporting two primary care physicians in separate locations. Providers serving the intervention group will have the capability to utilize relevant patient data with the electronic functionality to check protocol guidelines, electronically review home finger sticks, prescribe and check drug reference and automate verification of insurance eligibility and formulary status.

The Dia-Tech portable, innovative, integrated system generates standardized blood sugar reports, and furnishes notes to facilitate accurate evaluation of patient blood glucose, which are accessible upon demand to care providers.

Critical evaluation endpoints will include:
1) Improving glycosylated hemoglobin, weight, blood pressure, lipid levels, patient and physician satisfaction while improving adherence to clinical guidelines;
2) Reducing medication errors;
3) Improving clinical decisions for diabetic elderly.

Outcome:
The adoption of Telemedicine/Telepharmacy to clinical practice will improve implementation and adherence of evidence-based diabetes management for the elderly.

Extraction of Rat Skin Interstitial Fluid for Glucose Monitoring Using Glass Microneedles

Ping M. Wang*, Megan Cornwell, Mark R. Prausnitz

School of Chemical Engineering, Georgia Tech. Atlanta, GA 30332-0100

*IBB, 315 Ferst Dr. Georgia Tech., Atlanta, GA 30332
Tel: 404 385 1314 Fax: 404 894 2291
ping.wang@che.gatech.edu

For diabetes patients, it is painful and inconvenient to puncture themselves to collect blood samples for glucose monitoring using a syringe needle or lancet; therefore, it does not encourage patients to do more frequent testing. In this study, we developed alternatives to reduce the pain in blood sample collection. We fabricated hollow glass microneedles with tip diameters ranging 40-70 mm to penetrate into the skin of anesthetized hairless rats and extract interstitial fluid (ISF). The microneedle could be beveled for easy penetration. As much as 50 nano-liters of ISF could be extracted under the pressure of -200-500 mmHg within 10 min. The microneedle geometry and the ISF volume collected in its lumen space were quantified by digital video microscopy. In another experiment, we used non-beveled glass microneedles (the diameter at the tip ranged from 60 to 70 mm OD) to penetrate rat skin with a device for micropuncture we developed. This device could accurately control the puncture depth in the micron level. After puncturing the anesthetized rat's skin with 5-7 small holes, ranging from 150-250 mm in diameter, and the depth ranging from 200 to 500 mm, within the area of 1x1 cm2 at the chest, this area of skin was sucked at -200 mmHg for 10 min. The volume of the skin ISF extracted from each drilling hole ranged from 50-100 nl, which was enough for testing the ISF glucose levels using the FreeStyle TrackerTM glucose monitoring system. Our glass microneedle and the microneedle puncture device could be used at multiple sites of the body for glucose monitoring.
(Supported by ADA and NIH grants)

An *in vivo* Artificial Pancreas: How to Avoid Overcorrection Hypoglycemia

W. K. Ward*, M. D. Wood, M. J. Quinn, S. Pidikiti, A. Holland

*Corresponding author/presenter
Legacy Clinical Research and Technology Center
1225 NE 2nd Ave, Portland, OR 97232
Tel: 503.413.5171 • Fax: 503.413.4942
wkward@lhs.org

During closed loop glycemic control, insulin-induced correction of hyperglycemia can result in subsequent hypoglycemia, so avoidance of this problem was explored. Diabetes was created in rats by IP alloxan, 80-150 mg/kg and only those animals with Type 1 diabetes (serum ketones - > 1.5 mM after insulin omission) were studied further. Animals were implanted with a telemetric subcutaneous (SC) planar array of continuous glucose sensors, and data was transmitted every minute.

Every two weeks, SC insulin was omitted and a 6-hour closed loop study was performed with IV insulin. Blood glucose (BG) was obtained frequently and before closed loop insulin initiation was > 20 mM. The control algorithm was related to a proportional-integral-derivative system except that: (1) the algorithm was non-linear, (2) a differential exponential control system was used to quickly reduce the insulin infusion rate (IIR) when glycemic slope became negative, and (3) a cap was placed on the IIR.

There were 27 sensor closed loop studies in 4 animals. Early studies showed frequent overcorrection hypoglycemia. The IIR cap was then lowered to 1 unit/hr, which markedly reduced hypoglycemia. For the last 8 studies, BG during the final three hours averaged 7.9 mM, and duration of BG < 3.3 mM averaged only 10 min. Sensors performed well with minimal sensing delay.

We conclude that overcorrection hypoglycemia can be minimized by (1) using differential exponential control and (2) utilizing an insulin infusion rate cap. For artificial pancreas research, animals must have Type 1 diabetes verified by ketonemia or absence of C-peptide.

An Evaluation of a Diabetic Disease Management Program

Lynn White, MS, RN, FNP, CDE[1], Joanne M. Dalton, PhD, RN, CS,
Joanne Garvey, MA, RN, Doctoral Student

[1]Partners Home Care Inc, 200 Ledgewood Place, Rockland, MA 02337
781-681-1223
lwhite5@partners.org

Purpose: The first purpose of this program evaluation study is to test the utility of Orem's Self-Care Deficit Theory as a guide for Outcomes and Assessment Information Set (OASIS) outcomes research for home care-based disease management programs. Examination of the OASIS data items revealed close correspondence with certain concepts of Orem's theory, including the patient basic conditioning factors and power components that are fundamental to self-care agency. The second purpose of the study is to determine the outcomes of an experimental Diabetic Disease Management Program (DDMP) for home healthcare patients. Phase 1 of the study focuses on description of the patients and outcomes data for traditional home healthcare provided to diabetic home care patients prior to the implementation of the experimental DDMP and prior to the implementation of the HCFA-mandated Prospective Payment System (PPS). In Phase 2, patients outcomes after the implementation of PPS but prior to the implementation of the experimental DDMP are examined. In Phase 3, patient outcomes after the implementation of PPS and of the DDMP are examined.

Method: All OASIS and other relevant data will be collected retrospectively from medical records and computerized databases located at a large Visiting Nurse Association in New England. Study participants will be Diabetic Type 1 and Type 2 adult (18 years or older) patients who were admitted to and discharged from an episode of home healthcare services. Phase 1 study participants (n = 80-100) will be patients admitted to the agency between October 1, 1999 and October 1, 2000. Phase 2 study participants (n = 80-100) will be patients admitted to the agency between October 1, 2000 and March 31, 2001. Phase 1 and Phase 2 patients will have received the traditional diabetic home care program. Phase 3 study participants (n = 80-100) will be patients admitted to the agency between April 1, 2001 and August 31, 2001. Phase 3 patients will receive the experimental DDMP.

The variables are categorized according to selected concepts of Orem's theory. Nineteen variables that represent basic conditioning factors measure patient characteristics; 11 variables that represent power components measure the patient's ability to perform activities at the time of admission to the agency; 6 variables that represent nurse agency measure nurse characteristics, and 11 discharge clinical outcome variables that represent power components measure the patient's ability to perform activities at the time of discharge from the agency. One other discharge clinical outcome variable measures blood glucose level. Another 14 variables, including 2 emergent care variables, measure discharge utilization outcomes.

Data will be analyzed using descriptive, nonparametric, and parametric statistics. The level of significance is set at .05.

Results: The data are currently being collected and analyzed.

Point-of-Service Approach to Diabetic Patient Management: Improving Patient Care and Clinic Financial Performance

M. Wurster*, R. Kettelkamp

Saint Lukes Shawnee Mission Health System and Ohio State University

*Corresponding Author
5228 Bluff View, Parkville, MO, 64152
mwurster@kc.rr.com

Background: Diabetes afflicts approximately 17 million patients in the United States and is a major cause of morbidity and mortality. Proper care of patients with diabetes has been shown to reduce long-term complications. Yet large numbers of patients remain undiagnosed and untreated and many patients with diabetes receive inadequate or inappropriate treatment.

Problem: To provide improvements in the screening and quality of care given diabetic patients using a methodology that is still cost effective and practical in a primary care setting.

Purpose: To evaluate the clinical and financial impact of a combination of point-of-service (POS) testing, software decision support and workflow redesign with the management of diabetes therapy in a primary care setting.

Methods: The study sites are multi-specialty primary care clinics at metropolitan teaching hospitals. Ninety-five diabetic patients have been enrolled to date. Charts were reviewed on all diabetic patients receiving diabetic related care. Included in this study are those patients who were followed by the Multispecialty clinic during the year prior to the initiation of the experimental approach (baseline phase), and those who continued to receive care in the clinic a year after the new approach had been implemented (intervention phase). During the intervention phase, diabetic management included the use of a point-of-service device for real-time lab testing, as well as a computerized diabetic management system designed by the author to help reduce medical errors, streamline clinic workflow and aid in tracking patient outcomes.

Results: In January of 2001, a diabetes program utilizing a combined approach to point-of-service care was opened. With software application in a limited alpha test format, the program currently serves two half-day medical resident continuity clinic sessions per week. For diabetic patients in these clinic sessions, compliance rates with recommended maintenance guidelines are markedly higher than compliance rates for patients in other sessions. Examples are shown below:

	New Approach	Traditional Approach
HbgA1c	87%	13%
Lipid Profile	87%	12%
Urinalysis	75%	12%
Microalbumin	56%	0%
Eye exam	62%	6%
Foot exam	62%	0%
Pneumococcal vaccine	68%	25%

In the first three months, the program generated approximately $4850.00 in new revenue from 189 diabetes related interventions. Labor related costs have been reduced about 75%.

Conclusion: This innovative approach to diabetic management allows a primary care clinic to significantly improve diabetic patient care and compliance, while simultaneously improving the clinic's financial performance.
Clinical Implications: Work is ongoing to implement this approach in a multi-center trial. Use of point-of-service care could significantly reduce regional and, when widely implemented, national health care costs and improve quality of care for all diabetic patients.

CSII Gives Better Quality of Life and Satisfaction with Treatment in Parents of Both Children and Adolescents with Diabetes Type 1

B. Zdunczyk*, E. Pankowska, M. Lipka

*Department of Clinical Child and Adolescent Psychology, Warsaw, Poland
Clinical Child Hospital
ul. Dzialdowska 1/3, 01-184 WARSZAWA, POLAND
Tel: +48 22 4523289 Fax: +48 22 6322767
betaz@interia.pl

Introduction: The deterioration of the quality of life and the higher anxiety level is observed in patients with diabetes type 1 and their families. New methods of treatment (CSII) aim at improving medical care and the quality of life. The feeling of satisfaction in parents may be indirect measurement of patients' QOL (especially young children).
Aim: This study examined the feeling of satisfaction and anxiety level in parents of diabetic patients type 1 using different treatment (MDI vs. CSII).

Method: Subjects filled in the QOL and STAI questionnaires. N parents: 46 (22 CSII and 24 - MDI; Children age <2.5-18.0>; Mean = 10.2; N Children Age <10: CSII -12, MDI-10; N Adolescents: CSII-12, MDI-12). HbA1c and other variables were controlled.

Results: Parents CSII presented greater satisfaction with treatment no matter the child's age ($F=6.715$, $df=3$; $p<0.002$) and diabetes duration ($F=5.342$; $df=4$; $p<0.002$). Parents CSII are more satisfied with treatment of the child ($t=4.418$, $df=41$, $p<0.05$). Parents CSII are more satisfied with their life ($t=2.20$; $df=45$, $p<0.04$). There was no significant difference in the anxiety level. Mothers (N=36) are significantly less satisfied ($t=2.618$, $df=14$, $p<0.02$). The lower child's HbA1c level and CSII use - the greater satisfaction with life ($F=6.070$; $df=2$; $P<0.01$). The relationship between the anxiety level and the satisfaction with life was detected ($R2=070$; $p<0.05$).

Conclusions: CSII system gives better quality of life and greater satisfaction with treatment in parents of diabetic children. The higher anxiety level results in the lower satisfaction in life. The level of HbA1c affects the feeling of life satisfaction. CSII is recommended for the treatment of very young children.